

Report on Carcinogens

Twelfth Edition

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National Toxicology Program

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Report on Carcinogens

Introduction and NTP Report on Carcinogens Review Process

Introduction

The probability that a resident of the United States will develop cancer at some point in his or her lifetime is 1 in 2 for men and 1 in 3 for women (ACS 2010). Nearly everyone's life has been directly or indirectly affected by cancer. Most scientists involved in cancer research believe that the environment in which we live and work may be a major contributor to the development of cancer (Lichtenstein *et al.* 2000). In this context, the "environment" is anything that people interact with, including exposures resulting from lifestyle choices, such as what we eat, drink, or smoke; natural and medical radiation, including exposure to sunlight; workplace exposures; drugs; socio-economic factors that affect exposures and susceptibility; and substances in air, water, and soil (OTA 1981, IOM 2001). Other factors that play a major role in cancer development are infectious diseases, aging, and individual susceptibility, such as genetic predisposition (Montesano and Hall 2001). We rarely know what environmental factors and conditions are responsible for the onset and development of cancer; however, we have some understanding of how some types of cancer develop, especially cancer related to certain occupational exposures or the use of specific drugs. Many experts firmly believe that much of the cancer associated with the environment may be avoided (Tomatis *et al.* 1997).

The people of the United States, concerned about the relationship between their environment and cancer, have asked, through the U.S. Congress, for information about substances that are known or appear likely to cause cancer (i.e., to be carcinogenic). Section 301(b)(4) of the Public Health Service Act, as amended, provides that the Secretary of the Department of Health and Human Services shall publish a biennial report that contains the following information:

- A list of all substances (1) which either are known to be human carcinogens or may reasonably be anticipated to be human carcinogens and (2) to which a significant number of persons residing in the United States are exposed
- Information concerning the nature of such exposure and the estimated number of persons exposed to such substances.
- A statement identifying (1) each substance contained in this list for which no effluent, ambient, or exposure standard has been established by a Federal agency and (2) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in this list, the extent to which such standard decreases the risk to public health from exposure to the substance.
- A description of (1) each request received during the year to conduct research into, or testing for, the carcinogenicity of a substance and (2) how the Secretary and other responsible entities responded to each request.

The Report on Carcinogens (RoC) is an informational scientific and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances (hereinafter referred to as "substances") that may pose a hazard to human health by virtue of their carcinogenicity. For each listed substance, the RoC contains a substance profile which provides information on (1) the listing status, (2) cancer studies in humans and animals, (3) studies of genotoxicity (ability to damage genes) and biologic mechanisms, (4) the potential for human exposure to these substances, and (5) Federal regulations to limit exposures. The RoC does not present quantitative assessments of the risks of cancer associated with these substances. Thus, the listing of substances in the RoC only indicates a potential hazard and does not establish the exposure conditions that would pose cancer risks to individuals in their daily lives. Such formal risk

assessments are the responsibility of the appropriate Federal, state, and local health regulatory and research agencies.

The substances listed in the RoC are either known or reasonably anticipated to cause cancer in humans in certain situations. With many listed substances, cancer may develop only after prolonged exposure. For example, smoking tobacco is known to cause cancer in humans, but not all people who smoke develop smoking-related cancer. With some substances or exposure circumstances, however, cancer may develop after even brief exposure. Examples include certain occupational exposures to asbestos or bis(chloromethyl) ether. The cancer hazard that listed substances pose to any one person depends on many factors. Among these are the intrinsic carcinogenicity of the substance, the amount and duration of exposure, and the individual's susceptibility to the carcinogenic action of the substance. Because of these considerations, the RoC does not attempt to rank substances according to the relative cancer hazards they pose.

Potential Beneficial Effects of Listed Carcinogens

As stated above, the purpose of the RoC is to identify hazards to human health posed by carcinogenic substances; therefore, it is not within the scope of this report to address potential benefits of exposure to certain carcinogenic substances in special situations. For example, numerous drugs typically used to treat cancer or other medical conditions have been shown to increase the frequency of primary cancer (i.e., cancer located in the organ or tissue where it originated) or secondary cancer (i.e., cancer that has spread from its organ or tissue of origin to other parts of the body) in patients undergoing treatment for specific diseases. In these cases, the benefits of using the drug to treat or prevent a specific disease outweigh the added cancer risk associated with its use. Personal decisions concerning voluntary exposure to carcinogenic substances should be based on information that is beyond the scope of the RoC. Individuals should not make decisions concerning the use of a given drug, or any other listed substance, based solely on the information contained in the RoC. Such decisions should be made only after consultation with a physician or other appropriate specialist.

Identification of Carcinogens

For many years, government research agencies (including the National Toxicology Program), industries, academia, and other research organizations have studied various substances to identify those that may cause cancer. Much of the information on specific chemicals or occupational exposures has been published in the scientific literature or in publicly available and peer-reviewed technical reports. This literature is a primary source of information for identifying and evaluating substances for listing in the RoC. Many of the listed substances also have been reviewed and evaluated by other organizations, including the World Health Organization's International Agency for Research on Cancer (IARC), in Lyon, France, the Environmental Protection Agency of the State of California, and other U.S. Federal and international agencies.

Studies in both humans and experimental animals are used to evaluate whether substances are potentially carcinogenic in humans. Other studies that may elucidate possible mechanisms of action of potential carcinogens also are considered in the evaluations. The strongest evidence for establishing a relationship between exposure to any given substance and cancer in humans comes from epidemiological studies — studies of the occurrence of a disease in a defined human population and the factors that affect its occurrence (Hill 1971). Interpretation of epidemiological studies of human exposure and cancer can be difficult (Rothman 1986), as they must rely on natural, not experimental, human exposure and must therefore consider

many factors that may affect cancer prevalence in addition to the exposure under study. One such factor is the latency period for cancer development (i.e., the time between first exposure to a carcinogen and development of cancer). The first sign of cancer often appears many years (sometimes 20 to 30 years or more) after exposure to the carcinogen. Epidemiological studies of workers exposed to high levels of chemicals have led to the identification of many carcinogens in the United States (Fontham *et al.* 2009).

Another valuable method for identifying substances as potential human carcinogens is the long-term bioassay in experimental animals. These studies provide accurate information about dose and duration of exposure, and they are less affected than epidemiological studies by possible interactions of the test substance with other chemicals or modifying factors (Huff 1999). In these studies, the substance is given to one or (usually) two species of laboratory rodents over a range of doses for nearly the animals' entire lives. Experimental cancer research is based on the scientific assumption that substances causing cancer in animals will have similar effects in humans; however, it is not possible to predict with complete certainty from animal studies alone which substances will be carcinogenic in humans. Known human carcinogens have also been shown to cause cancer in experimental animals when tested adequately (Fung *et al.* 1995). In many cases, a substance first was found to cause cancer in animals and later confirmed to cause cancer in humans (Huff 1993, 1999). How experimental animals respond to substances, including developing cancer or other illnesses, does not always strictly correspond to how people will respond. Nevertheless, experimental animal studies remain the best tool for detecting potential human health hazards of all kinds, including cancer (OTA 1981, Tomatis *et al.* 1997).

In addition to the use of studies in humans and experimental animals, alternative testing methods that incorporate advances in molecular toxicology, computational sciences, and information technology are being developed to prioritize substances for carcinogenicity testing and reduce the use of animals in testing. A 2007 report by the National Academy of Science's National Research Council, *Toxicity Testing in the 21st Century*, outlined strategies for new approaches, and a research collaboration among the National Toxicology Program (NTP), the U.S. Environmental Protection Agency (EPA), and the National Institutes of Health Chemical Genomics Center was established to evaluate whether high-throughput and computational toxicology approaches can yield data that predict the results of toxicity studies in experimental animals. The results should facilitate prioritization of chemicals for further testing, as well as enable more effective predictions of carcinogenic risk of substances to humans (Collins *et al.* 2008).

Listing Criteria

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are shown in the box on this page. The listing criteria presented here were first adopted for use in the *Eighth Report on Carcinogens*, which was published in 1998. The listing criteria were clarified the following year in two *Federal Register* notices (NTP 1999a,b). Listing criteria for substances listed in earlier editions of the RoC are outlined in the introductions to those editions.

Preparation of the RoC

The Secretary of the Department of Health and Human Services has delegated the responsibility for the preparation of the RoC to the NTP. The process used to prepare the RoC involves several levels of scientific review and opportunities for public comment on the substances considered for listing in or delisting (removal) from the RoC. For the *Twelfth Report on Carcinogens*, the NTP revised the RoC re-

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans,* which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans,* which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question, which can be useful for evaluating whether a relevant cancer mechanism is operating in humans.

view process to enhance the scientific development of the report and address guidance in the Office of Management and Budget's *Final Information Quality Bulletin for Peer Review* (OMB 2004). Two important new elements in the RoC review process are (1) public peer review of draft background documents by *ad hoc* scientific expert panels and (2) public peer review of draft substance profiles by the NTP Board of Scientific Counselors. (See NTP Report on Carcinogens Review Process, below, for details of the process.)

Estimation of Exposure

The RoC is required to list only substances to which a significant number of people living in the United States are exposed. Some substances that have been banned or restricted in use (e.g., safrole, arsenical pesticides, and mirex) are listed either because people who

were previously exposed remain potentially at risk or because these substances still are present in the environment.

The RoC is also required to provide information about the nature of exposures and the estimated numbers of people exposed to listed substances. Four of the agencies participating with the NTP in preparation of the *Twelfth Report on Carcinogens*—the Consumer Product Safety Commission (CPSC), EPA, U.S. Food and Drug Administration (FDA), and Occupational Safety and Health Administration (OSHA)—are responsible for regulating hazardous substances and limiting the exposure to and use of such substances. Because little information typically is available, estimating the number of people who could be exposed and the route, intensity, and duration of exposure for each substance is a difficult task. However, other types of information, such as data on use, production, and occupational or environmental exposure, can be used to determine whether there is (or was) exposure in the United States, and this information is included in each substance profile. The National Institute for Occupational Safety and Health (NIOSH) has conducted two occupational exposure surveys: the National Occupational Hazard Survey (NOHS), conducted from 1972 to 1974, and the National Occupational Exposure Survey (NOES), conducted from 1981 to 1983. These surveys yielded data on potential exposure to many listed substances. Although dated, NOES estimates are provided in the profiles of the listings when available, and NOHS figures are provided if no other exposure data are available.

Regulations and Guidelines

The RoC is required to identify each of the listed substances for which no standard for exposure or release into the environment has been established by a Federal agency. The RoC addresses this requirement by providing in each profile a summary of the regulations and guidelines, if any, that are likely to decrease human exposure to that substance. Some of these regulations and guidelines have been enacted for reasons other than the substance's carcinogenicity (e.g., to prevent adverse health effects other than cancer or to prevent accidental poisoning of children). These regulations are included in the profiles because reduction of exposure to a suspected or known carcinogen is likely to reduce the risk for cancer. Regulations are organized by regulatory agencies and the acts enforced by those agencies, and are provided at the end of each profile.

The majority of the regulations cited in the RoC were enacted by the following Federal agencies: CPSC, the U.S. Department of Transportation, EPA, FDA, and OSHA. The guidelines cited in the RoC primarily are those published by NIOSH and the American Conference of Governmental Industrial Hygienists. In addition, regulations and guidelines enacted by other governmental agencies are cited if their likely outcome is to reduce exposure to the substance. It is beyond the scope of this report to provide detailed information or interpretation concerning the implementation of each regulatory act, and no attempt is made to do so. Some commonly used regulatory terms are defined in the Glossary, which follows the Substance Profiles. Links to the Web sites for the *Code of Federal Regulations* and for each of the major regulatory agencies are provided at the end of the Reference section of this Introduction for those wishing to obtain additional information on these agencies and their regulations.

Two regulations that apply to all substances listed in the RoC and whose purpose is to reduce exposure to the listed substances were identified; however, because they apply to every substance listed in the RoC, they are not identified individually in the listing profiles but are described below:

- OSHA's Hazard Communication Standard. This regulation is intended to communicate the hazards of chemicals and

appropriate protective measures to protect employees. The program includes maintenance of a list of hazardous chemicals, labeling of containers in the workplace, and preparation and distribution of material safety data sheets to employees. The rule states that a chemical shall be considered "hazardous" if it has been listed as a carcinogen or potential carcinogen in current editions of (1) the NTP's RoC, (2) the IARC Monographs, or (3) OSHA's Occupational Safety and Health Standards, Subpart Z—Toxic and Hazardous Substances.

- EPA's Criteria for the Evaluation of Permit Applications for Ocean Dumping of Materials under the Toxic Substances Control Act. This regulation prohibits ocean dumping of materials containing "known carcinogens, mutagens, or teratogens or materials suspected to be carcinogens, mutagens, or teratogens by responsible scientific opinion" as other than trace contaminants.

Two OSHA regulations identified in some of the listing profiles require clarification:

- Specific substances are listed as having "comprehensive standards" if, in addition to the permissible exposure limit (PEL), OSHA has regulations for the substance that include provisions for exposure monitoring, engineering and work practice controls, use of respirators and protective garments and equipment, hygiene facilities, information and training, labeling of substance containers and worker areas in which the substance is used, and health screening programs. The sets of comprehensive standards are provided in 29 CFR 1910 Subpart Z and also on the OSHA Web site.
- The OSHA PEL identified in the profiles for Certain Glass Wool Fibers (Inhalable), Ceramic Fibers (Respirable Size), and Wood Dust are based on the standard for Particulates Not Otherwise Regulated (PNOR). This standard sets limits applicable to all inert or nuisance dusts, whether mineral, inorganic, or organic, not identified specifically by substance name. OSHA recommended that the profiles for these three substances include the PEL established by the PNOR standard.

Cancer Rates and Estimates of Risk Reduction

Cancer is the second leading cause of death in the United States. According to estimates from the American Cancer Society, there were over 1.5 million new cancer cases and over 560,000 deaths from cancer in the United States in 2009 (Gapstur and Thun 2010). In men, the most common sites of newly diagnosed cancer are the prostate, lung and bronchus, and colorectum (colon and rectum); these three sites account for 52% of all cancer cases, and prostate cancer is the most common (28%). In women, the three most common sites, accounting for 52% of the total, are the breast (28%), lung and bronchus, and colorectum. At present, cancer at these sites also results in the highest death rates: in men, mortality is highest for cancer of the lung and bronchus, followed by the prostate and colorectum; in women, mortality is highest for cancer of lung and bronchus, followed by the breast and colorectum (Jemal *et al.* 2010). Data on cancer incidence and death rates were reported in the "Annual Report to the Nation on the Status of Cancer, 1975–2006" (Edwards *et al.* 2010) and "Cancer Statistics, 2010," prepared annually by the American Cancer Society (Jemal *et al.* 2010); both reports use the most recent data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER 2010).

In recent years, there have been modest decreases in overall cancer incidence rates (0.5% per year in women from 1998 to 2006 and 1.3% per year in men from 2000 to 2006) and death rates (1.5% per

year from 2002 to 2006 in women and 2% per year from 2001 to 2006 in men) (Edwards *et al.* 2010, Jemal *et al.* 2010). These decreases are largely explained by decreased rates of colorectal, prostate, and lung cancer in men and breast and colorectal cancer in women. Mortality from lung cancer in women has stabilized since 2003, after increasing for many years (Jemal *et al.* 2010). In contrast, mortality from other types of cancers has been increasing. The largest increases in death rates have been for liver cancer in men and women, esophageal cancer and melanoma in men, and lung and pancreatic cancer in women (Jemal *et al.* 2010). Incidence rates have increased for (1) kidney cancer, melanoma of the skin, and leukemia in men and women, (2) myeloma and cancer of the esophagus and liver in men, and (3) cancer of the lung, thyroid, pancreas, and urinary bladder, and non-Hodgkin's lymphoma in women (Edwards *et al.* 2010). Of particular concern is that incidence rates of cancer in children have been increasing; rates are highest among infants and then decline until around age 9, after which the rates increase with age. For 2010, the American Cancer Society estimated that there would be 10,700 new cancer cases in children under the age of 14 (all races combined). Leukemia (31%) and brain cancer (21%) account for over half of diagnosed cases of childhood cancer (Jemal *et al.* 2010). Children are particularly vulnerable to environmental risk factors, including numerous toxins and detrimental exposures from air, food, water, medicines, pesticides, and ionizing radiation, even before birth (NCI 2010).

The World Health Organization predicts that by 2030, 12 million deaths worldwide will be due to cancer; however, 30% to 40% of these deaths are considered to be preventable (WHO 2009). Approaches to reduction of cancer incidence and mortality include both primary prevention, including the reduction or elimination of exposure, and secondary prevention, including early detection via screening and treatment of any diagnosed precancerous conditions or early malignancies (Bode and Dong 2009). Reduction of tobacco use over the past 50 years is largely responsible for the decrease in lung-cancer mortality in men. About 40% of the decrease in overall cancer mortality in men is due to decreased lung-cancer mortality, indicating that primary prevention has a major impact in improving public health (Jemal *et al.* 2010). For example, a combination of education and social policies, such as excise taxes and smoke-free air laws, contribute to reducing tobacco use. Mortality from lung cancer has not yet decreased in women because cigarette smoking in women peaked 20 years later than in men. Decreases in mortality from cervical, breast, and colon cancer are thought to have resulted from a combination of early detection and improvements in treatment, although reduction in the use of menopausal hormone therapy among post-menopausal women starting in 2001 may also have contributed to decreases in breast-cancer incidence.

Primary prevention is the basis of current regulatory policies that aim to lower human exposure to cancer-causing substances and thereby improve public health. It is reasonable and prudent to accept that reducing exposure for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer in humans (Tomatis *et al.* 1997, Montesano and Hall 2001). For each effluent, ambient, or exposure standard established by a Federal agency for a listed substance, the RoC is required to state the extent to which, on the basis of available medical, scientific, or other data, the implementation of that standard decreases the public's risk for cancer. This statement requires quantitative information on how much protection from cancer the public is afforded by established Federal standards. Estimating the extent to which listing a substance in the RoC protects public health is perhaps the most difficult task in preparing the RoC. The carcinogenic risk depends on many things, including the intensity, route, and duration of exposure to a

carcinogen. People may respond differently to similar exposures, depending on their age, sex, nutritional status, overall health, genetics, and many other factors. Only in a few instances can risk for cancer be estimated with complete confidence, and these estimations require studies of long-term human exposures and cancer incidence in restricted environments, which rarely are available. However, there is evidence that regulations have led to the reduction in exposure to a number of substances listed in the RoC and probably have contributed, in part, to the decreases in cancer incidence and mortality observed over the past decade. The reduction in cancer death rates translates to the prevention of approximately 767,000 deaths over the 16-year period from 1990 to 2006 (Jemal *et al.* 2010). For example, major environmental pollution prevention acts, such as EPA's Resource Conservation and Recovery Act, Clean Water Act, and Clean Air Act, were passed in the early 1970s. These laws have led to reduced exposure to a number of pollutants. Although no analyses were found to determine whether these regulations have decreased cancer incidences, analyses have shown that they have reduced premature deaths from respiratory illnesses and heart attacks (EPA 2010). Studies have shown associations between lung-cancer mortality and air pollution; therefore, it seems reasonable that regulations reducing air pollution have also reduced cancer risks (Montesano and Hall 2001, Raaschou-Nielsen *et al.* 2010). U.S. workplace levels of many occupational carcinogens also have been reduced since the 1970s (Fontham *et al.* 2009), and it therefore is presumed that these reductions have prevented occupationally related cancers.

Listing of Substances in the Twelfth Report on Carcinogens

Each edition of the RoC is cumulative and includes substances newly reviewed in addition to those listed in previous editions. The *Twelfth Report on Carcinogens* contains 240 substance profiles, some of which (e.g., Estrogens, Steroidal) consist of a class of structurally related chemicals or agents. These include 54 profiles for substances listed as *known to be human carcinogens* and 186 profiles for substances listed as *reasonably anticipated to be human carcinogens*. Profiles for related exposures, such as exposure to various types of ultraviolet radiation, and selected members of chemical families, such as nitroarenes, are often grouped together. There are six new listings and two revised listings. Of the six newly listed substances, Aristolochic Acids are listed as known to be human carcinogens, and Captafol, Cobalt-Tungsten Carbide: Powders and Hard Metals, *o*-Nitrotoluene, Riddelliine, and Styrene are listed as reasonably anticipated to be human carcinogens. Formaldehyde, which was first listed in the *Second Annual Report on Carcinogens* in 1981 as reasonably anticipated to be a human carcinogen, is now listed as known to be a human carcinogen. Certain Glass Wool Fibers (Inhalable) was first listed as Glass Wool (Respirable Size) in the *Seventh Annual Report on Carcinogens* (1994) as reasonably anticipated to be a human carcinogen; although the classification remains the same, the review of Glass Wool Fibers has resulted in a change in the scope of the listing.

Immediately following a description of the NTP Report on Carcinogens Review Process (below), the names of all the substances — agents, substances, mixtures, or exposure circumstances — listed in the RoC are given in alphabetical order for the two listing categories. Part A identifies the substances listed in the RoC as *known to be human carcinogens*, and Part B identifies those listed as *reasonably anticipated to be human carcinogens*. The substance profiles are arranged in alphabetical order and contain (1) a brief description of each substance, with a summary of the evidence for its carcinogenicity, (2) relevant information on properties, use, production, and exposure, and (3) a summary of the regulations and guidelines that are likely to decrease

exposure to the substance. The profiles include references to scientific literature used to support the listings. The substances listed in the RoC do not include all human carcinogens. The RoC lists only those nominated agents, substances, mixtures, or exposure circumstances for which relevant data exist and have been reviewed and found to meet the listing criteria defined above. As additional substances are nominated, they will be considered and reviewed for possible listing in future editions of the RoC.

Other Information Provided in the Twelfth Report on Carcinogens

Following the Substance Profiles, additional information is provided about terms that are used frequently in the profiles, including a Glossary, a list of Acronyms and Abbreviations, and Units of Measurement. In addition, the following appendices are provided:

- Appendix A provides a list of manufacturing processes, occupations, and exposure circumstances classified by IARC as carcinogenic to humans.
- Appendix B lists the agents, substances, mixtures, or exposure circumstances that have been delisted from the RoC.
- Appendix C lists the agents, substances, mixtures, or exposure circumstances that have been reviewed but not recommended for listing in the RoC.
- Appendix D identifies participants who collaborated in preparation of the *Twelfth Report on Carcinogens*.
- Appendix E is a table of chemicals that have been nominated to the NTP for toxicological or carcinogenicity testing since 2004.
- Appendix F is a cross-referenced list of substances and their common synonyms or abbreviations.
- Appendix G lists, by Chemical Abstract Service (CAS) Registry number, all of the chemicals included in the RoC for which CAS Registry numbers were identified.

The *Twelfth Report on Carcinogens* was prepared following procedures that maximized the quality, objectivity, utility, and integrity of the information contained in the report. Although not anticipated, factual errors or omissions in this report may be identified after its distribution. If this should happen, these errors or omissions will be addressed by the NTP. Where appropriate, corrections will initially be posted on the NTP RoC Center Web site at <http://ntp.niehs.nih.gov/go/roc> and then made in the next edition of the RoC. For more information on the published *Twelfth Report on Carcinogens*, including how to request a printed or electronic copy or to access it on the Internet, visit the NTP RoC Center Web site at the link provided above or contact Dr. Ruth Lunn, Director, Report on Carcinogens Center, National Toxicology Program, MD K2-14, P.O. Box 12233, Research Triangle Park, NC 27709; telephone (919) 316-4637; fax (919) 541-0144; e-mail lunn@niehs.nih.gov.

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Web Sites

- American Conference of Governmental Industrial Hygienists (ACGIH)
<http://www.acgih.org/home.htm>
- Code of Federal Regulations (CFR), U.S. Government Printing Office
<http://www.gpoaccess.gov/cfr/index.html>
- Consumer Product Safety Commission (CPSC)
<http://www.cpsc.gov>
- Department of Transportation (DOT)
<http://www.dot.gov>
- Environmental Protection Agency (EPA)
<http://www.epa.gov>
- Integrated Risk Information System: <http://cfpub.epa.gov/ncea/iris/index.cfm>
- Food and Drug Administration (FDA)
<http://www.fda.gov>
- Center for Food Safety & Applied Nutrition: <http://www.cfsan.fda.gov>
- International Agency for Research on Cancer (IARC).
<http://www.iarc.fr>
- Monographs on the Evaluation of Carcinogenic Risks of Chemicals to Humans
<http://monographs.iarc.fr/index.php>
- National Institute for Occupational Safety and Health (NIOSH)
<http://www.cdc.gov/niosh>
- Pocket Guide to Chemical Hazards: <http://www.cdc.gov/niosh/npg>
- NIOSH Safety and Health Topic – Cancer: <http://www.cdc.gov/niosh/topics/cancer>
- NIOSH Carcinogen List: <http://www.cdc.gov/niosh/topics/cancer/npotocca.html>
- National Toxicology Program (NTP)
<http://ntp.niehs.nih.gov>
- Report on Carcinogens: <http://ntp.niehs.nih.gov/go/roc>
- Occupational Safety and Health Administration (OSHA)
<http://www.osha.gov>

NTP Report on Carcinogens Review Process

The Report on Carcinogens (RoC) is a Congressionally mandated document that identifies and discusses agents, substances, mixtures, or exposure circumstances (collectively referred to as “substances”) that may pose a hazard to human health by virtue of their carcinogenicity. Substances are listed in the report as either *known* or *reasonably anticipated to be human carcinogens*. The National Toxicology Program (NTP) prepares the RoC on behalf of the Secretary of Health and Human Services (HHS). The RoC review process is described below and consists of four major parts: (1) nominations and selection of candidate substances, (2) scientific review of candidate substances, (3) peer review of draft substance profiles, and (4) preparation of the RoC and transmittal to Congress and the public. A schematic of the RoC review process is provided at the end of this section.

Nominations and Selection of Candidate Substances

The NTP invites nominations for consideration for listing in the RoC from anyone in the public and private sectors. Nominations may seek to list a new substance in the RoC, reclassify the listing status for a substance already listed, or remove a substance already listed. Nominations should be submitted to the NTP¹ at <http://ntp.niehs.nih.gov> select “Provide Input to NTP.” Nominations must contain a rationale or reason for the review and, if possible, appropriate background information and relevant data (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer Monographs, exposure surveys, and release inventories) to support the rationale.

The NTP initially evaluates each nomination to determine whether the scientific information available for a nomination justifies its formal review and consideration. Those nominations proposed for review proceed as discussed below. The reason for not going forward with review of a new nomination would be the lack of sufficient information² for applying the listing criteria³ (see Introduction). The reason for not proceeding with a nomination to reclassify or remove a current listing would be the absence of significant new scientific information published since the original listing. Those nominations not selected for review are returned to the original nominator who is invited to resubmit the nomination with additional information such as new data, exposure information, etc. that justifies a formal review. The NTP may defer or terminate the review of a proposed nomination at any time if relevant information becomes available that warrants the NTP’s reconsideration of the substance’s review. In such cases, the nominator, the NTP Board of Scientific Counselors (BSC),⁴ the NTP Executive Committee,⁵ and the public would be notified of this action.

The NTP announces nominations proposed for review and solicits public comments through announcements in the *Federal Register* and NTP publications. These announcements ask for relevant information concerning carcinogenicity of the substance as well as data on current production and information on exposure and patterns of use. Comments received in response to the public announcements

are used to (1) refine the list of nominated substances to identify the candidate substances that will proceed through the full review process and (2) identify scientific issues that should be addressed in the preparation and/or review of the draft background document for an individual candidate substance. In addition, the NTP invites the public to nominate scientists to serve on an expert panel⁶ for each specific candidate substance. An expert panel will be convened to provide peer review of the draft background document, make a recommendation for the candidate substance’s listing status in the RoC, and provide the scientific justification for that recommendation.

Scientific Review of Candidate Substances

The scientific review of a candidate substance consists of three major steps: (1) preparation of the draft background document, (2) review by an expert panel at a public meeting, and (3) internal review by two independent federal committees.

Draft Background Documents

The NTP prepares a draft background document for each candidate substance under consideration. The background documents may be prepared with the assistance of a consultant(s) with expertise and/or knowledge relevant to the specific candidate substance. Background documents are prepared following the general format presented below. Background documents do not contain any opinion regarding the listing status for the candidate substance. Data used to prepare Sections 3 through 5 must come from publicly available, peer-reviewed sources.

1. Introduction

This section describes the properties (e.g., chemical, physical or biological) of the candidate substance and states the scientific rationale for review. For chemicals, it contains the following sections (1) chemical identification, including synonyms, trade names, CAS Registry numbers, molecular formula, and molecular structure, (2) physical-chemical properties, and (3) identification of structural analogues or metabolites. For other types of agents (e.g., biological, exposure circumstances, or physical), it provides appropriate information to define the candidate substance.

2. Human Exposure

This section provides a summary of relevant data documenting both present and past exposures. It typically provides information on use, production, environmental occurrence, and exposure (including release and fate in air, water, soil, and food), exposure to the general population (e.g., occurrence in consumer products or medical devices), occupational exposure, biological indices of exposure, and regulations and guidelines to limit exposure.

3. Human Cancer Studies

This section summarizes traditional cancer epidemiology studies (mainly case-control and cohort studies, but may also include descriptive studies and case reports). Data from clinical studies may also be included.

¹National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

²Lack of sufficient information means that adequate studies (such as animal, human, or mechanistic), which are critical for evaluation of the carcinogenicity of the nomination, are not currently available in the peer-reviewed literature.

³The criteria for listing a substance in the RoC are available at <http://ntp.niehs.nih.gov> see “Report on Carcinogens.”

⁴The BSC is a federally chartered advisory committee whose members are appointed by the Secretary, HHS. The BSC provides advice to the NTP Director on matters relating to scientific program content and evaluates the scientific merit of the NTP’s intramural and collaborative programs.

⁵The NTP Executive Committee is composed of the heads (or their designees) of federal research and regulatory agencies and provides advice to the NTP on policy issues.

⁶An expert panel is an *ad hoc* group of scientists with relevant expertise and knowledge selected by the NTP from the public and private sectors. Nominations to serve on specific expert panels are solicited from federal and nonfederal sources. The final selections for membership are based upon providing a balanced and unbiased group of highly qualified individuals and are made in accordance with the Federal Advisory Committee Act and HHS implementing regulations.

4. Studies in Experimental Animals

This section summarizes experimental animal studies of potential carcinogenesis including long term bioassays, subchronic studies, initiation and promotion studies, and studies of known metabolites.

5. Other Relevant Data

This section discusses the available, relevant mechanistic and other scientific information that would be needed to understand the toxicity and potential carcinogenicity of the candidate substance and that would be useful for evaluating the carcinogenic potential of the substance in people. For a specific substance, it may include information on (1) absorption, distribution, excretion and metabolism, (2) genetic damage and related effects, (3) mechanistic studies and considerations, (4) toxicity, and (5) the carcinogenicity and mutagenicity of structural analogues.

When the initial draft is completed, the NTP posts the draft background document on the RoC Web site. Availability of the draft background document is announced on the NTP listserv and in other NTP publications. Draft background documents are also available on compact disks or in hardcopy upon request (see Contact Information, below).

Expert Panel Meeting

The NTP convenes an expert panel for each candidate substance. The NTP publishes a *Federal Register* notice at least 60 days prior to the expert panel meeting announcing the meeting and availability of the draft background document. The public is invited to attend this meeting and provide oral and/or written comments on the draft background document. The public may also provide opinion on the listing status for the candidate substance. All comments received within this time period become part of the public record that will be reviewed by the expert panel and are posted on the RoC Web site. The expert panel is first charged to peer review the background document. Once the peer review is complete, the NTP asks the expert panel (1) to apply the RoC listing criteria to the relevant scientific evidence and make a recommendation regarding the listing status for the candidate substance and (2) to provide the scientific justification for that recommendation. The expert panel will also submit a report that contains (1) its peer review comments on the draft background document and (2) its recommendation for listing in the RoC and the scientific justification for that recommendation. The NTP will post the expert panel's report on the RoC Web site and publish a *Federal Register* notice inviting comment on the expert panel's recommendation for listing status and the scientific justification for that recommendation. The NTP will also prepare a response to the expert panel's peer review comments on the draft background document that will be made available to the public on the RoC Web site upon release of the RoC.

Following the expert panel meeting, NTP staff reviews and considers the expert panel's peer review comments and any public comments as it finalizes the background document on the candidate substance. The final version of the background document is then posted on the RoC Web site. Availability of the final background document and the expert panel report is announced through the NTP listserv.

Internal Reviews by the Government

Following the expert panel meeting, the NTP goes through a number of reviews that are internal to the government to develop an initial listing status for each candidate substance to the RoC. The internal review process is closed to the public and consists of separate meetings of two groups: (1) an interagency scientific review group (ISRG)

and (2) the NIEHS/NTP scientific review group (NSRG). Both groups are provided with all relevant information (including the background document, the expert panel report, and any public comments received to date) on the candidate substances and asked to apply the listing criteria to this information and make a recommendation on the listing status of the candidate substance.

Peer Review of Draft Substance Profiles

Taking into consideration the listing recommendations of the expert panel, the NSRG, and the ISRG, and the public comments, the NTP prepares a draft substance profile¹ with a listing recommendation for each candidate substance. Once the draft substance profile is developed, the NTP convenes a meeting of the BSC to peer review the draft substance profiles for candidate substances to the RoC. The NTP publishes a *Federal Register* notice at least 60 days prior to the BSC meeting announcing the meeting and the availability of the draft substance profiles. The public is invited to attend this meeting and provide oral and/or written comments on the draft substance profiles. All comments received within this time period become part of the public record for review by the BSC and posted on the RoC Web site. The NTP makes available to the BSC all relevant information. The BSC is charged to determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated and supports the NTP's policy decision regarding its listing in the RoC. The BSC is not asked to review the NTP's decision regarding listing status. The BSC prepares and submits a peer review report to the NTP that describes the nature and scope of its findings and conclusions concerning the NTP's draft substance profiles.

Preparation of Draft RoC and Transmittal

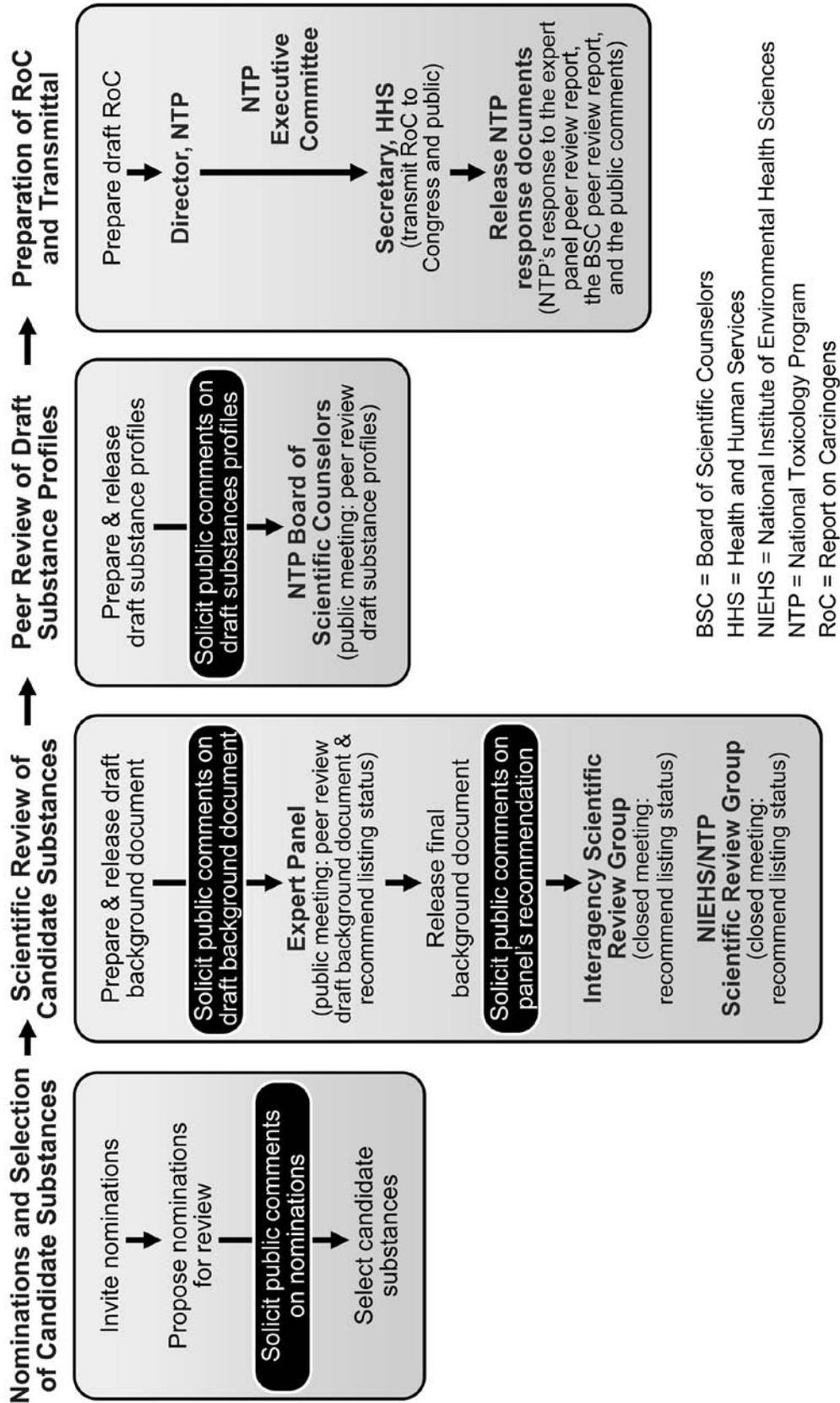
The NTP responds to the peer review report and drafts the next edition of the RoC. The draft RoC is submitted to the NTP Director for review. The Director distributes the draft RoC to the NTP Executive Committee for consultation, review, and comment. Following approval of the draft RoC by the Director, a final draft of the RoC is prepared and submitted to the Secretary, HHS for review and approval. Upon approval of the RoC, the Secretary transmits it to the U.S. Congress, and the report is published and disseminated to the public. The NTP publishes a notice in the *Federal Register* and NTP publications that announces availability of the report and identifies the listing outcome for each candidate substance that underwent formal review for the RoC. At this time, the NTP posts the BSC's peer review report, the NTP's response to that report, and the NTP's response to the expert panel peer review comments on the draft background documents on the RoC Web site. In addition, for the *Twelfth Report on Carcinogens*, the NTP will prepare a response to public comments received on candidate substances since issuance of the expert panel report² and will post the response on the RoC Web site.

The NTP makes the latest edition of the RoC available electronically on the NTP RoC Web site (<http://ntp.niehs.nih.gov> and select "Report on Carcinogens"), on compact disk, and in printed form. For information on how to request a printed or electronic copy, contact Dr. Ruth M. Lunn.

¹The RoC contains substance profiles for each candidate substance. Full substance profiles are developed for substances *known or reasonably anticipated to be human carcinogens* and contain the listing status, summarize the scientific information that supports the recommendation, and provide information on use, exposure and production. Limited substance profiles are developed for candidate substances not listed in or delisted from the RoC, which vary in content on a case-by-case basis.

²The NTP's preparation of a response to public comments will be done on a trial basis for the *Twelfth Report on Carcinogens*. The NTP will assess the merit of responding to public comments following completion of the *Twelfth Report on Carcinogens* and determine whether any change is needed in the review process with regard to this practice.

NTP Report on Carcinogens Review Process



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NTP Listserv

The NTP listserv is an e-mail distribution list used to disseminate information on NTP activities. To subscribe, visit <http://ntp.niehs.nih.gov> and select "Contact Us."

Report on Carcinogens

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Listing Status

Substance Profiles

Glossary

Acronyms and Abbreviations

Units of Measurement

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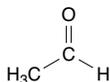
Acetaldehyde

CAS No. 75-07-0

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as ethanal



Carcinogenicity

Acetaldehyde is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to acetaldehyde by inhalation caused tumors in two rodent species and at two different tissue sites. In rats of both sexes, it caused cancer of the nasal mucosa (squamous-cell carcinoma and adenocarcinoma), and in hamsters of both sexes, it caused cancer of the larynx (carcinoma) (IARC 1985, 1987). Inhalation of acetaldehyde also promoted the induction of respiratory-tract tumors by intratracheal instillation of the known carcinogen benzo[*a*]pyrene in hamsters of both sexes.

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens*, an additional study in rats has been identified. Administration of acetaldehyde in drinking water increased the incidences of hemolymphoreticular cancer (leukemia and lymphoma combined), benign tumors of the pancreas (islet-cell adenoma), and cancer of the bone (osteosarcoma) and nasal cavity (carcinoma) in males and benign mammary-gland tumors (fibroma or fibroadenoma) in females (Soffritti *et al.* 2002). Increased incidences of tumors observed at other sites occurred only at one of the lower doses tested.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acetaldehyde. A survey of workers producing acetaldehyde and other aldehydes in Germany reported 9 cases of cancer, including 5 of lung cancer and 2 of oral-cavity cancer, among an unspecified number of workers; these incidences reportedly were higher than expected, but the observations were confounded by the fact that all cases of cancer occurred in tobacco smokers (IARC 1985, 1987).

Since acetaldehyde was listed in the *Sixth Annual Report on Carcinogens*, additional epidemiological studies have been identified, primarily case-control studies of populations exposed to acetaldehyde (the main initial metabolite of alcohol) following consumption of alcoholic beverages. Alcoholic beverage consumption is listed in the Report on Carcinogens as *known to be a human carcinogen*. In its 1999 review, the International Agency for Research on Cancer noted that three small case-control studies found increased risks of alcohol-related cancer (of the oral cavity, pharynx, larynx, and esophagus) among individuals with genetic variations (polymorphisms) that result in increased levels of acetaldehyde after alcohol consumption. However, IARC concluded that the data available were inadequate to evaluate the carcinogenicity of acetaldehyde (IARC 1999). Since then, a number of review articles and meta-analyses have summarized the results of subsequent studies that found dose-response relationships between alcohol consumption and cancer of the oral cavity, pharynx, larynx, and esophagus, and possibly the stomach and colon, among individuals with genetic polymorphisms that in-

crease blood or salivary levels of acetaldehyde (Bagnardi *et al.* 2001, Zeka *et al.* 2003, Boffetta and Hashibe 2006, Baan *et al.* 2007, Boccia *et al.* 2009, Salaspuro 2009). In 2009, IARC concluded that acetaldehyde associated with alcohol consumption was carcinogenic to humans (Secretan *et al.* 2009). Few studies have been conducted on the association of these polymorphisms with cancer at other tissue sites, and the role of acetaldehyde in pancreatic, liver, bladder, or breast cancer is not clear (van Dijk *et al.* 2001, Terry *et al.* 2006, Seitz and Becker 2007, Visavanathan *et al.* 2007, Druesne-Pecollo *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

Alcohol is metabolized to acetaldehyde by alcohol dehydrogenases (ADH), and acetaldehyde is metabolized to acetic acid by aldehyde dehydrogenases (ALDH). In some individuals, genetic polymorphisms in these enzymes can result in either higher rates of acetaldehyde production from alcohol or lower rates of acetaldehyde metabolism to acetic acid, resulting in higher blood acetaldehyde levels after a given level of alcohol intake than in individuals without these polymorphisms. Five ADH genes have been identified in humans, two of which have been shown to be polymorphic. The variant allele of the *ALDH2* gene, which is prevalent in Asians, encodes an enzyme that has almost no ability to detoxify acetaldehyde (IARC 1999).

Properties

Acetaldehyde is an aliphatic aldehyde that exists at room temperature as a colorless gas with a fruity, pungent odor. It is miscible with water, ether, benzene, gasoline, solvent naphtha, toluene, xylene, turpentine, and acetone. It is very flammable and is unstable in air (Akron 2009, HSDB 2009). Physical and chemical properties of acetaldehyde are listed in the following table.

Property	Information
Molecular weight	44.0 ^a
Specific gravity	0.79 at 16°C/4°C ^a
Melting point	-124°C ^a
Boiling point	21°C ^a
Log <i>K</i> _{ow}	-0.34 ^b
Water solubility	1,000 g/L at 25°C ^a
Vapor pressure	902 mm Hg at 25°C ^a
Vapor density relative to air	1.5 ^a
Dissociation constant (p <i>K</i> _a)	13.6 at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Acetaldehyde is used primarily as a chemical intermediate in the production of acetic acid, pyridine and pyridine bases, peracetic acid, pentaerythritol, butylene glycol, and chloral. It is also used in the synthesis of crotonaldehyde, flavor and fragrance acetals, acetaldehyde 1,1-dimethylhydrazone, acetaldehyde cyanohydrin, acetaldehyde oxime, various acetic acid esters, paraldehyde, metaldehyde (a molluscicide widely used to kill slugs and snails), polymers, and various halogenated derivatives (IARC 1985, 1999). Acetaldehyde has been used in the manufacture of aniline dyes, plastics, and synthetic rubber, to silver mirrors, and to harden gelatin fibers. It has also been used in the production of polyvinyl acetal resins, in fuel compositions, to inhibit mold growth on leather, and in the manufacture of disinfectants, pesticides, drugs, explosives, lacquers and varnishes, photographic chemicals, phenolic and urea resins, and rubber accelerators and antioxidants (EPA 1994).

Acetaldehyde is considered by the U.S. Food and Drug Administration to be generally recognized as safe for use as a flavoring agent and adjuvant (Furia and Bellanca 1975, HSDB 2009). It is an important component of food flavorings and is added to milk products, baked

goods, fruit juices, candy, desserts, and soft drinks; it is especially useful for imparting orange, apple, and butter flavors. The concentration of acetaldehyde in food generally is up to 0.047%. In 1976, about 8,600 kg (19,000 lb) of acetaldehyde was used as food additives. Acetaldehyde is also used in the manufacture of vinegar and as a fruit and fish preservative. It is approved for use in phenolic resins in molded containers for contact with non-acidic foods. Acetaldehyde is no longer registered as an active ingredient in any pesticide. When it was used as a fumigant for storage of apples and strawberries, it was exempted from a residue tolerance (IARC 1985, EPA 1994, HSDB 2009).

Production

Acetaldehyde was first produced commercially in 1916 (IARC 1985). U.S. production was 63.5 million kilograms (140 million pounds) in 1940 and 408 million kilograms (899 million pounds) in 1960. Production peaked in 1969 at 748 million kilograms (1.65 billion pounds), decreasing to 281 million kilograms (619 million pounds) in 1982. In 2009, acetaldehyde was produced by 50 manufacturers worldwide (17 in China, 12 in India, 6 in East Asia, 5 in Europe, 5 in Central and South America, 2 in Mexico, 2 in the Middle East, and 1 in the United States) (SRI 2009) and was available from 49 suppliers, including 21 U.S. suppliers (ChemSources 2009). U.S. imports of acetaldehyde increased from 1,000 kg (2,200 lb) in 1989 to 414,000 kg (913,000 lb) in 2006 (USITC 2009). U.S. exports of acetaldehyde were 19 million kilograms (42.6 million pounds) in 1989, decreasing to 1.6 million kilograms (3.5 million pounds) in 2003 and remaining near this level from 2004 through 2008 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of acetaldehyde totaled 500 million to 1 billion pounds in 1986 and 1990 and 100 million to 500 million pounds in 1994, 1998, and 2002 (EPA 2004).

Exposure

There is high potential for exposure of the general population to acetaldehyde through ingestion, inhalation, and dermal contact and of workers through inhalation and dermal contact. The main source of exposure of the general population is through consumption of alcoholic beverages and the subsequent metabolism of alcohol to form acetaldehyde (HSDB 2009). Because acetaldehyde may form in wine and other alcoholic beverages after exposure to air (Hagemeyer 2002), alcoholic beverages (including wines, beer, and spirits) also frequently contain acetaldehyde as a volatile component (HSDB 2009).

Acetaldehyde is a product of most hydrocarbon oxidation reactions and is a normal intermediate in the respiration of most higher plants. It is found in trace amounts in many plant products, including apples, broccoli, coffee, grapefruit, grapes, lemons, mushrooms, onions, oranges, peaches, nectarines, pears, pineapples, raspberries, strawberries, cranberries, sour cherries, and mango. It has been detected in the essential oils of alfalfa, rosemary, balm, clary sage, dafodil, bitter orange, camphor, angelica, fennel, mustard, peppermint, and lychee, and in oak and tobacco leaves and cotton leaves and blossoms (IARC 1985, Burdon *et al.* 1996, Gorny *et al.* 1999, Gunes *et al.* 2002, Bonerz *et al.* 2007, Mahattanatawee *et al.* 2007). Acetaldehyde has also been detected in breast milk. Consumers may be exposed to acetaldehyde in many milk products, including all types of cheese, yogurt, and milk of varying fat content (Mistry and Hassan 1992, Barbieri *et al.* 1994, Jandal 1996, Beshkova *et al.* 1998, Van Aardt *et al.* 2001, Kondyli *et al.* 2002, Boscaini *et al.* 2003, Di Cagno *et al.* 2004, Fernandez-Garcia *et al.* 2004, Blagden and Gilliland 2005, Gadaga *et al.* 2007, Kaminarides *et al.* 2007). Acetaldehyde has also been detected in cooked beef, chicken, and fish (HSDB 2009, Yasuhara and

Shibamoto 1995) and is used as a synthetic flavoring ingredient in processed foods, especially margarine (HSDB 2009).

According to EPA's Toxics Release Inventory, environmental releases of acetaldehyde have increased slightly since 1988, when 9.5 million pounds was released, 73% to air, 23% to underground injection wells, and the remainder to surface water and landfills. Since then, releases to underground injection wells have decreased, and releases to surface water have increased. In 2007, 11.4 million pounds of acetaldehyde was released from 336 facilities that processed, produced, or used the chemical; 29 facilities each released more than 100,000 lb. Of the total amount, 94% was released to air, 3.1% to underground injection wells, and 2.8% to water (TRI 2009). Acetaldehyde will volatilize rapidly from water or land, and it will leach into the ground, where it will biodegrade (HSDB 2009). Acetaldehyde is also degraded readily in soil, sewage, and natural waters by microorganisms (EPA 1987).

Acetaldehyde is a natural product of photooxidation of hydrocarbons commonly found in the atmosphere and occurs naturally as emissions from forest fires, volcanoes, and animal wastes. In the 1990s, annual emissions of acetaldehyde from all sources in the United States were estimated at 12.1 million kilograms (27 million pounds) (IPCS 1995). Burning wood produces acetaldehyde at approximately 0.7 g/kg of wood, and fireplace emissions range from 0.083 to 0.20 g/kg of wood burned (HSDB 2009). In the 1990s, annual emissions from residential burning in the United States were estimated at 5,000 metric tons (11 million pounds) (IPCS 1995). Acetaldehyde is also a combustion product of some plastics (e.g., polycarbonate) and some hard and soft polyurethane foams. It also occurs in gasoline exhaust (1.4 to 8.8 mg/m³) and diesel exhaust (0.05 to 6.4 mg/m³); however, very little is emitted from small engines such as lawn mowers or leaf blowers (IARC 1985, Baldauf *et al.* 2006).

Many individuals are exposed to acetaldehyde by inhalation. The highest ambient-air concentrations of acetaldehyde were reported for urban or suburban areas or near sources of combustion (HSDB 2009). In ambient air, concentrations of acetaldehyde generally averaged 5 µg/m³. Indoor air concentrations were higher than ambient concentrations in all locations where acetaldehyde air concentrations were measured, both in the United States and in other countries (Miguel *et al.* 1995, Mukund *et al.* 1996, Brickus *et al.* 1998, MacIntosh *et al.* 2000, Possanzini *et al.* 2002, Baez *et al.* 2003, Hellen *et al.* 2004, Hodgson *et al.* 2004, Park and Ikeda 2004, Saijo *et al.* 2004, Sax *et al.* 2004, Shendell *et al.* 2004, Gilbert *et al.* 2005, Cavalcante *et al.* 2006, Ohura *et al.* 2006, Pang and Mu 2006, Sax *et al.* 2006, Hodgson *et al.* 2007, Possanzini *et al.* 2007). Acetaldehyde is also found in tobacco and marijuana cigarette smoke (1,220 µg per cigarette) and tobacco cigarettes (980 to 1,370 µg per cigarette).

In 1988–89, acetaldehyde was detected in 4 of 10 surveyed water supplies (EPA 1987). In surface water, concentrations generally are less than 0.1 µg/L, and the contribution from drinking water to human exposure is considered negligible (IPCS 1995).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 216,533 workers, including 97,770 women, potentially were exposed to acetaldehyde (NIOSH 1990). Workers potentially exposed include those involved in the manufacture or use of industrial organic chemicals, dyes, fabricated rubber, plastics, urea-formaldehyde foam insulation, fuels, drugs, explosives, varnishes, pesticides, food additives, leather goods, and mirrors (IARC 1985, EPA 1994).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acetaldehyde on ships and barges.

Department of Transportation (DOT)

Acetaldehyde is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)**Clean Air Act**

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of acetaldehyde is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of acetaldehyde = U001.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 200 ppm (360 mg/m³).

Considered a highly hazardous chemical: Threshold quantity (TQ) = 2,500 lb.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – ceiling (TLV-C) = 25 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,000 ppm.

Listed as a potential occupational carcinogen.

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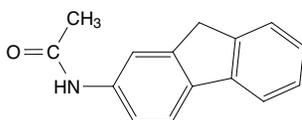
2-Acetylaminofluorene

CAS No. 53-96-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 2-acetamidofluorene, N-2-fluorenylacetylamide, or N-fluoren-2-yl-acetamide



Carcinogenicity

2-Acetylaminofluorene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-acetylaminofluorene caused tumors at several different tissue sites in mice and rats. Dietary administration of 2-acetylaminofluorene caused cancer of the liver (hepatocellular carcinoma) and urinary bladder (transitional-cell carcinoma) in female mice (Staffa and Mehlman 1980) and in rats of both sexes (Wilson *et al.* 1941). In rats, it also caused skin cancer (carcinoma, possibly arising from the auditory canal).

Since 2-acetylaminofluorene was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. In female mice, dietary administration of 2-acetylaminofluorene caused mammary-gland cancer (adenocarcinoma), as well as urinary-bladder cancer (transitional-cell carcinoma) (Greenman *et al.* 1987). In rats, dietary administration of 2-acetylaminofluorene caused liver cancer (hepatocellular carcinoma or cholangiocarcinoma) in both sexes, mammary-gland cancer (adenocarcinoma) in females, and tumors of the testes (mesothelioma of the tunica vaginalis) and Zymbal gland in males (Weisburger *et al.* 1981, Cabral and Neal 1983). A single subcutaneous injection of 2-acetylaminofluorene caused liver tumors (hepatocellular tumors) in newborn male mice (Fujii 1991). Liver tumors were also observed following dietary administration of 2-acetylaminofluorene to male dogs (Allison *et al.* 1950) and to fish of both sexes (hepatocellular tumors or cholangiocarcinoma) (Pliss and Khudoley 1975) and following addition of 2-acetylaminofluorene to the tank water of fish of unspecified sex (hepatocellular adenoma or carcinoma) (James *et al.* 1994). In hamsters of both sexes, intratracheal instillation of 2-acetylaminofluorene caused urinary-bladder cancer (transitional-cell carcinoma) (Oyasu *et al.* 1973). Intraperitoneal injection of 2-acetylaminofluorene in newborn hamsters until weaning, followed by dietary administration, caused cancer of the urinary bladder (carcinoma) and liver (cholangiocarcinoma) and benign stomach tumors (squamous-cell papilloma) (Oyasu *et al.* 1972, Matsumoto *et al.* 1976).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-acetylaminofluorene.

Properties

2-Acetylaminofluorene is an aromatic amine that occurs as a tan crystalline powder at room temperature (Akron 2009). It is practically insoluble in water, but is soluble in glycols, alcohols, ether, acetic acid, and fat solvents (HSDB 2009). 2-Acetylaminofluorene is stable at normal temperatures and pressures, but when heated to decomposition, it produces irritating or toxic gases (e.g., nitrogen oxides, carbon monoxide, carbon dioxide, hydrogen fluoride) (Akron 2009). Physical and chemical properties of 2-acetylaminofluorene are listed in the following table.

Property	Information
Molecular weight	223.3 ^a
Density	1.27 g/cm ^{3b}
Melting point	194°C ^a
Boiling point	303°C ^c
Log K _{ow}	3.22 ^a
Water solubility	144 mg/L at 25°C ^a
Vapor pressure	9.44 × 10 ⁻⁸ mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

2-Acetylaminofluorene is used as a research tool, primarily as a positive control in studies of the carcinogenicity and mutagenicity of other chemicals (HSDB 2009). 2-Acetylaminofluorene was intended for use as a pesticide, but it was never marketed, because of its carcinogenicity in experimental animals.

Production

2-Acetylaminofluorene is not currently produced in commercial quantities in the United States or anywhere else in the world (SRI 2009). One U.S. producer of 2-acetylaminofluorene was reported in 1977, but production volume was not reported (TSCA 1979). In 2009, 2-acetylaminofluorene was distributed by 17 specialty chemical companies, including 11 in the United States (ChemSources 2009). These distributors typically sell 2-acetylaminofluorene in small quantities, and total estimated U.S. usage is low.

Exposure

The routes of potential human exposure to 2-acetylaminofluorene are inhalation, ingestion, and dermal contact (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of 2-acetylaminofluorene increased from 9,800 lb in 1998 to 81,000 lb in 2001, declined to a low of 255 lb in 2003, and have remained below 1,000 lb since 2003. Most of the releases were to hazardous-waste landfills. In 2007, one facility released about 500 lb of 2-acetylaminofluorene to a hazardous-waste landfill and about 250 lb to air (TRI 2009). The risk of occupational exposure to 2-acetylaminofluorene is greatest for chemists, chemical stockroom workers, and biomedical researchers. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 373 workers potentially were exposed to 2-acetylaminofluorene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-acetylaminofluorene = U005.

Listed as a hazardous constituent of waste.

Mine Safety and Health Administration

To control airborne exposure, 2-acetylaminofluorene shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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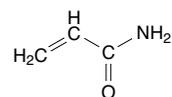
Acrylamide

CAS No. 79-06-1

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as 2-propenamide



Carcinogenicity

Acrylamide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Acrylamide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Administration of acrylamide in the drinking water caused benign thyroid-gland tumors (follicular-cell adenoma) in rats of both sexes. In male rats, it also caused tumors of the lining of the testes (mesothelioma of the tunica albuginea) and benign adrenal-gland tumors (pheochromocytoma). In female rats, it also caused cancer of the uterus (adenocarcinoma), benign and malignant tumors of the mammary gland (adenoma and adenocarcinoma), and benign tumors of the pituitary gland (adenoma), oral cavity (papilloma), and clitoral gland (ade-

noma). In strain A/J mice (a strain with a high spontaneous incidence of lung cancer), administration of acrylamide by stomach tube or by intraperitoneal injection increased both the incidence of benign lung tumors (adenoma) and number of tumors per animal in both sexes. In initiation-promotion studies, acrylamide administered dermally, by stomach tube, or by intraperitoneal injection followed by long-term dermal exposure to the tumor promoter 12-*O*-tetradecanoylphorbol-13-acetate induced benign and malignant skin tumors (squamous-cell papilloma and carcinoma) in female mice (IARC 1986).

Cancer Studies in Humans

Most of the available epidemiological studies of cancer and exposure to acrylamide have been published since acrylamide was listed in the *Sixth Annual Report on Carcinogens*. In a study of a multi-plant cohort consisting mostly of male workers, the incidence of pancreatic cancer was significantly higher among workers with the highest cumulative exposure to acrylamide than in the U.S. population. Among exposed workers, the incidence of pancreatic cancer was significantly associated with duration of exposure and time since first exposure (Marsh *et al.* 1999, Schulz *et al.* 2001). In a follow-up of this cohort, the relative risk of pancreatic cancer increased with increasing duration of exposure after adjustment for smoking, but the trend was not statistically significant, and no clear trends were observed for cumulative or average exposure (Marsh *et al.* 2007). A small cohort study of U.S. workers (mostly male) found statistically nonsignificant increases in the risks for cancers of the digestive system, including pancreatic cancer (Sobel *et al.* 1986, Swaen *et al.* 2007).

Several population-based studies that investigated the association between dietary intake of acrylamide and specific cancer outcomes were reviewed by Hogervorst *et al.* (2010). Several prospective cohort studies used case-cohort or nested case-control analyses to evaluate dietary exposure to acrylamide (based on a food-frequency questionnaire) and the risks of cancer at specific tissue sites; these include the Swedish Women's Lifestyle and Health Cohort, the Swedish Mammography Cohort, the Netherlands Study on Diet and Cancer, a cohort of Swedish men, the U.S. Nurses' Health Study, and the Danish Diet, Cancer, and Health Study. In addition, several case-control studies (most of which used food-frequency questionnaires) assessed cancer and dietary exposure of Swedish, French, and U.S. populations to acrylamide. The tissue site studied most frequently was the breast. These studies found no overall association between breast cancer and dietary exposure to acrylamide; however, some, but not all, studies reported an association between acrylamide exposure and a specific type of breast cancer (sex-hormone-receptor-positive cancer in post-menopausal women). The Danish study used acrylamide-hemoglobin adducts to assess exposure; however, these adducts are not source-specific, but reflect both dietary exposure and exposure from other sources, such as smoking. Two of three prospective cohort studies reported increased risks of endometrial and ovarian cancer, but a case-control study found no increased risk of ovarian cancer. Most of the studies evaluating prostate and colorectal cancer did not find increased risks associated with dietary exposure to acrylamide. Findings were mixed for cancer of the kidney, head, and neck, and evaluation of cancer at other tissue sites was limited by the small numbers of studies.

Properties

Acrylamide is an unsaturated amide that exists as a white, odorless crystalline solid at room temperature. It is soluble in water, methanol, ethanol, acetone, ethyl acetate, and chloroform, and insoluble in benzene and heptane. Acrylamide is stable under normal conditions but may decompose or polymerize when heated or exposed to ultra-

violet light (Akron 2009). When heated to decomposition, acrylamide emits acrid fumes and nitrogen oxides (HSDB 2009). Commercial acrylamide monomer contains residual levels of acrylonitrile (1 to 100 mg/kg) (IARC 1986). Residual acrylamide monomer is present in the polymer at approximately 0.01% (Fujiki *et al.* 1984, IARC 1986). Physical and chemical properties of acrylamide are listed in the following table.

Property	Information
Molecular weight	71.1
Specific gravity	1.122 at 30°C/4°C
Melting point	84.5°C
Boiling point	192.6°C
Log K_{ow}	-0.67
Water solubility	371 g/L at 20°C
Vapor pressure	7×10^{-3} mm Hg at 25°C
Vapor density relative to air	2.5

Source: HSDB 2009.

Use

Acrylamide is a chemical intermediate used in the production and synthesis of polyacrylamides that can be modified to develop non-ionic, anionic, or cationic properties for specific uses. These water-soluble polymers can be used as additives for water treatment, enhanced oil recovery, flocculants, papermaking aids, thickeners, soil-conditioning agents, sewage and waste treatment, ore processing, and permanent-press fabrics (Habermann 2002). In 2001, 94% of acrylamide was used to produce polyacrylamide, of which 56% was used for water treatment, 24% for pulp and paper production, 10% for mineral processing, 4% for miscellaneous uses, and the remaining 6% for production of *N*-methylolacrylamide and other monomers (CMR 2002). Acrylamide is also used in the synthesis of dyes, in copolymers for contact lenses, and in the construction of dam foundations, tunnels, and sewers (Habermann 2002).

The U.S. Food and Drug Administration has regulated the use of acrylamide and polyacrylamide in foods (IARC 1994). Acrylamide polymers containing less than 0.2% monomer may be used in food-packaging adhesives, paper, and paperboard; to wash or peel fruits and vegetables; and in gelatin capsules. In acrylamide polymers added to water for steam that will contact food, the monomer should not exceed 0.05% by weight.

Production

In 2002, four U.S. producers of acrylamide reported a production capacity of 301 million pounds (CMR 2002). In 2009, acrylamide was produced by 30 manufacturers worldwide, including 4 in the United States (SRI 2009), and was available from 55 suppliers, including 28 U.S. suppliers (ChemSources 2009). The demand for acrylamide increased from 191 million pounds in 2000 to 200 million pounds in 2001 (CMR 2002). In 1972, U.S. imports of acrylamide were considered negligible (HSDB 2009). Imports totaled 6.8 million kilograms (15 million pounds) in 1992, 2 million pounds in 2001, 2.9 million kilograms (6.4 million pounds) in 2007, and 2.6 million kilograms (5.8 million pounds) in 2008. U.S. exports of acrylamide were less than 0.9 million kilograms (2 million pounds) in 1992, 11 million pounds in 2000, and 8 million pounds in 2001; no more recent data on exports were found (EPA 1994, CMR 2002, USITC 2009). Reports filed from 1988 to 2006 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of acrylamide totaled 100 million to 500 million pounds except in 1990, when the quantity was 50 million to 100 million pounds (EPA 2004, 2009).

Exposure

The potential routes of human exposure to acrylamide are ingestion, dermal contact, and inhalation (Manson *et al.* 2005). Acrylamide has been found in a number of food products. In 2002, a Swedish study reported that acrylamide was formed in heated foodstuffs, especially potato products and other baked or fried high-carbohydrate foodstuffs (Tareke *et al.* 2002). The acrylamide content of food items is directly related to the amount of reducing sugars and asparagine in the raw product and the cooking temperature used in the preparation (Pedreschi *et al.* 2004). Studies have quantified acrylamide content in foods such as potato chips (up to 3,700 µg/kg), French fries (up to 12,000 µg/kg), cereal (up to 1,346 µg/kg), bread (biscuits and crackers, up to 3,200 µg/kg), gingerbread (up to 1,660 µg/kg), nuts and nut butters (up to 457 µg/kg), and coffee (up to 16 µg/L) (Friedman 2003, Andrzejewski *et al.* 2004, Hoenicke *et al.* 2004, Aguas *et al.* 2006). Average U.S. daily dietary intake for all individuals over the age of two years was estimated at 0.43 µg/kg of body weight; however, the estimated exposure of children aged two to five years was 1.06 µg/kg (Manson *et al.* 2005).

Acrylamide may also be ingested in drinking water contaminated by polyacrylamide flocculants used in water treatment (Brown *et al.* 1980a, Howard 1989). Residual acrylamide concentrations in 32 polyacrylamide flocculants approved for water-treatment plants ranged from 0.5 to 600 ppm (Howard 1989). Acrylamide remains in water after flocculation with polyacrylamides because it is very water soluble and is not readily adsorbed by sediment (Brown *et al.* 1980b, Howard 1989).

Dermal exposure to acrylamide may result from trace quantities in cosmetic products, gardening products, paper and pulp products, coatings, and textiles resulting from the use of polyacrylamide in these products (Manson *et al.* 2005). Acrylamide has been measured in body and hand lotions, powders, and creams at concentrations of up to 1,200 µg/kg, and daily exposure to acrylamide through cosmetic products was estimated at 0.95 µg/kg of body weight per day. Acrylamide also has been measured in mainstream cigarette smoke at concentrations of up to 2.34 µg per cigarette, which would result in an average daily intake of 0.67 µg/kg of body weight per day (based on a body weight of 70 kg) for a person smoking one pack a day.

Acrylamide may be released into the environment in waste from acrylamide production and the manufacture of polyacrylamides and other polymers (Howard 1989). The most important environmental contamination results from the use of acrylamide in soil grouting (IPCS 1985). Acrylamide is also released to water from acrylamide-based sewer grouting and wastepaper recycling (Brown *et al.* 1980a, 1982, Howard 1989). In 2005, EPA's Toxics Release Inventory reported environmental releases of 8,797,482 lb of acrylamide from 42 facilities, 99.9% of which was released to underground injection wells, and most of the rest to air (TRI 2009).

Because the vapor pressure of acrylamide is low, the monomer is not expected to occur in the vapor phase in air. Acrylamide biodegrades in surface water in approximately 8 to 12 days (Howard 1989). Acrylamide degradation in a secondary sewage plant would be complete in approximately 10 days; however, acrylamide has been detected in effluent from sewage treatment plants (HSDB 2009). Certain debris organisms that exist in anaerobic, light aerobic, or dark aerobic conditions in natural and polluted environments are able to degrade acrylamide (Brown *et al.* 1980b). Acrylamide is highly mobile in aqueous environments; it thus readily leaches into soil and is carried great distances in groundwater of deep rock aquifers, where it will not be biodegraded (IPCS 1985). Bioconcentration of acrylamide is unlikely, because it degrades easily in surface waters and is highly water soluble (Manson *et al.* 2005). In an EPA study of five industrial

sites of acrylamide and polyacrylamide production and one site of polyacrylamide use, the highest concentration of acrylamide in water was found downstream from a polyacrylamide producer, at 1.5 mg/L (IPCS 1985, Howard 1989). In this study, the average acrylamide concentration was less than 0.2 µg/m³ in air and less than 0.02 mg/kg in soil and sediment (IPCS 1985).

Occupational exposure to acrylamide is primarily from dermal contact with the solid monomer and inhalation of dust and vapor during acrylamide and polyacrylamide production. The highest exposure occurs during the handling of the monomer. In two acrylamide manufacturing plants, breathing-zone concentrations were 0.1 to 3.6 mg/m³. During normal operations, workers at another plant were exposed to concentrations of up to 0.3 mg/m³ (IARC 1986). At U.S. acrylamide production facilities, the mean concentration of acrylamide in air was 640 µg/m³ in packing areas (Manson *et al.* 2005). In other parts of the world, acrylamide-hemoglobin adducts were used to estimate occupational exposure. In China, the highest acrylamide adduct concentration was 34,000 pmol/g of globin, found in the blood of workers in an acrylamide and polyacrylamide manufacturing plant. Occupationally exposed German smokers had adduct concentrations of up to 85 pmol/g of hemoglobin. In tunnel workers exposed to polyacrylamide in grout, acrylamide adducts were found at concentrations of up to almost 17,000 pmol/g (IARC 1986). Occupational exposure to acrylamide in aqueous form occurs mainly during maintenance and repair operations and connection and disconnection of equipment for transport. Routine exposure is minimal in captive production operations (Klaassen 1986). Improvements in the polymerization process have reduced the monomer content of the nonpotable-water-grade polymers from 5% to 0.3% (Brown *et al.* 1982).

Workers in the paper and pulp, construction, foundry, oil-drilling, textiles, cosmetics, food-processing, plastics, mining, and agricultural industries also are potentially exposed to acrylamide (Manson 2005). The potential for exposure is higher among grouters than other workers, because of the uncontrolled nature of the exposure; however, exposure levels have not been reported for grouters (IPCS 1985). The National Institute for Occupational Safety and Health estimated in 1976 that about 20,000 workers potentially were exposed to acrylamide (IARC 1986), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 10,651 workers potentially were exposed (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acrylamide solution on ships and barges.

Department of Transportation (DOT)

Acrylamide is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of acrylamide is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 5,000 lb.

Threshold planning quantity (TPQ) = 1,000 lb for solids in powder form with particle size < 100 µm or solution or molten form; = 10,000 lb for all other forms.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of acrylamide = U007, K014.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Each public water system must certify annually that when acrylamide is used in drinking-water systems, the level does not exceed 0.05% dosed at 1 mg/L (or equivalent).

Food and Drug Administration (FDA)

Acrylamide and various acrylamide copolymers may be used as food additives permitted for direct addition to food for human consumption, indirect food additives, secondary direct food additives, and food additives permitted in feed and drinking water of animals, as prescribed in 21 CFR parts 172, 173, 175, 176, 177, 178, and 573.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.3 mg/m³.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted-average (TLV-TWA) = 0.03 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.03 mg/m³.

Immediately dangerous to life and health (IDLH) limit = 60 mg/m³.

Listed as a potential occupational carcinogen.

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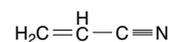
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Acrylonitrile

CAS No. 107-13-1

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Acrylonitrile is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Acrylonitrile caused tumors at several different tissue sites in rats. Exposure to acrylonitrile in drinking water or by inhalation caused cancer of the central nervous system (microglioma or glioma) and Zymbal gland (carcinoma) and benign tumors of the forestomach (squamous-cell papilloma or acanthoma) in both sexes (IARC 1979).

Since acrylonitrile was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Oral exposure to acrylonitrile caused cancer of the forestomach (squamous-cell carcinoma) and increased the combined incidence of benign and malignant Harderian-gland tumors (adenoma and carcinoma) in mice of both sexes. Benign and malignant tumors of the ovary (granulosa-cell tumors) and lung (alveolar/bronchiolar adenoma and carcinoma) in female mice also may have been related to acrylonitrile exposure (NTP 2001). In rats, prenatal exposure followed by postnatal inhalation exposure to acrylonitrile caused brain tumors

(glial-cell tumors) in both sexes. In females, it also caused cancer of the mammary gland and the blood vessels (angiosarcoma); in males, it caused cancer of the Zymbal gland and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) (IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to acrylonitrile. An increased risk of cancer of the lung and colon was reported in U.S. textile plant workers exposed to acrylonitrile and observed for 20 years or more (IARC 1979).

Since acrylonitrile was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. In studies of workers exposed to acrylonitrile (including textile workers and rubber workers) published in the 1980s and 1990s, including several meta-analyses, the risk of cancer was increased only for lung cancer among workers with the highest cumulative exposure levels in a large National Cancer Institute cohort study (IARC 1999). An update of a U.S. textile-worker cohort followed for five decades found no association between acrylonitrile exposure and cancer at any tissue site (Symons *et al.* 2008). A large international case-control study of lung cancer found a significant smoking-adjusted risk of lung cancer with increasing acrylonitrile exposure (Scélo *et al.* 2004), and a meta-analysis of lung-cancer findings found increased risk with acrylonitrile exposure after adjusting for a healthy-worker effect (Sponsiello-Wang *et al.* 2006). A small cohort study (Czeizel *et al.* 2004) found no excesses of lung or other cancer among workers possibly exposed to acrylonitrile; however, the study's statistical power to detect effects was limited. In an update of a cohort study in the Netherlands, excesses of brain cancer were found in some exposure categories (Swaen *et al.* 2004).

Properties

Acrylonitrile exists at room temperature as a volatile, flammable colorless liquid with a sweet characteristic odor. It is soluble in water and isopropyl alcohol and miscible with ethanol, carbon tetrachloride, ethyl acetate, ethylene cyanohydrin, xylene, toluene, petroleum ether, and liquid carbon dioxide. Acrylonitrile is stable under normal shipping and handling conditions but may undergo explosive polymerization if not inhibited (Akron 2009). Physical and chemical properties of acrylonitrile are listed in the following table.

Property	Information
Molecular weight	53.1
Specific gravity	0.8004 at 25°C/4°C
Melting point	-82°C
Boiling point	77.3°C at 760 mm Hg
Log K_{ow}	0.25
Water solubility	74.5 g/L at 25°C
Vapor pressure	109 mm Hg at 25°C
Vapor density relative to air	1.8

Source: HSDB 2009.

Use

Acrylonitrile is an important industrial chemical used extensively in the manufacture of synthetic fibers, resins, plastics, elastomers, and rubber for a variety of consumer goods, such as textiles, drinking cups, automotive parts, and appliances (Brazdil 2010). It is also used as a monomer for acrylic and modacrylic fibers, in plastics, in surface coatings, as a chemical intermediate, in organic synthesis, in home furnishings, in nitrile rubbers, and as a modifier for natural polymers (HSDB 2009). Of total acrylonitrile production, reported uses

were 38% for the production of adiponitrile, 22% for acrylonitrile-butadiene-styrene and styrene-acrylonitrile resins, 17% for acrylic fibers, 11% for acrylamide, 3% for nitrile elastomers, and 9% for miscellaneous uses, including polymers, polyols, barrier resins, and carbon fibers (CEN 2009). Acrylonitrile is used in the manufacture of carbon fibers used to reinforce composites for high-performance applications in the aircraft, defense, and aerospace industries. Other specialty applications include the production of fatty amines, ion-exchange resins, and fatty amine amides used in cosmetics, adhesives, corrosion inhibitors, and water-treatment resins (IARC 1999). Acrylonitrile was formerly used as a fumigant; however, almost all pesticide registrations for acrylonitrile were canceled in 1978 (ATSDR 1990).

Production

Acrylonitrile has been produced in the United States since 1940 (IARC 1979). It was ranked among the 50 highest-volume chemicals for several years (CEN 2009). U.S. production of acrylonitrile averaged 2.7 billion pounds from 1985 to 1987 and totaled 2.7 billion pounds in 1990 and 2.5 billion pounds in 1993. Production increased to 3.4 billion pounds in 1996 (IARC 1999), but had decreased to 2.2 billion pounds by 2008 (CEN 2009). In 2009, acrylonitrile was produced by 32 companies worldwide, including 5 in the United States (SRI 2009), and was available from 16 U.S. suppliers (ChemSources 2009). In 2000, U.S. imports of acrylonitrile exceeded 17 million pounds; since then, imports have decreased and have varied widely, from a low of 26,000 lb in 2004 to a high of 1.1 million pounds in 2008. U.S. exports of acrylonitrile exceeded 1.5 billion pounds in 2000 and reached a high of almost 3 billion pounds in 2004 (USITC 2009).

Exposure

The potential routes of human exposure to acrylonitrile are inhalation, ingestion, and dermal contact. Exposure is greater in occupational settings than in the general population. The general population may be exposed through the use of consumer products made with polymers of acrylonitrile, such as acrylic carpeting or polyacrylonitrile-resin-based food packaging. However, exposure from these sources is very low, because little of the monomer migrates from such products into air or food (ATSDR 1990). The U.S. Consumer Product Safety Commission in 1978 estimated concentrations of acrylonitrile as less than 1 ppm in acrylic and modacrylic fibers, 30 to 50 ppm in acrylonitrile-butadiene-styrene copolymers, 15 ppm in styrene-acrylonitrile copolymers, and 0 to 750 ppm in nitrile rubber and latex goods (as cited in IPCS 1983). Foods most likely to contain measureable acrylonitrile are high-fat or highly acidic items, such as luncheon meat, peanut butter, margarine, vegetable oil, or fruit juice. In 1984, typical concentrations of acrylonitrile in margarine were reported to be 25 µg/kg (ATSDR 1990). However, the U.S. Food and Drug Administration's Total Diet Study found no acrylonitrile residue in any of the foods tested from 1991 to 2004 (FDA 2006).

Acrylonitrile has been measured in the vapor phase of mainstream tobacco smoke at a concentration of 18.5 µg per cigarette (Laugesen and Fowles 2005). Indoor air concentrations of acrylonitrile in the residences of smokers (to which nonsmokers were exposed) were estimated at 0.5 to 1.2 µg/m³ (Nazaroff and Singer 2004). Acrylonitrile-hemoglobin adducts are a reliable marker of smoking behavior and correlate with the number of cigarettes smoked per day (Bergmark 1997, Fennell *et al.* 2000). The adducts may also be present in infants born to mothers who smoke (Tavares *et al.* 1996, Schettgen *et al.* 2004).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, the volume of environmental releases of acrylo-

nitrile has remained high since 2001, when 11.5 million pounds was released, and most releases since 2000 have been to underground injection wells. In 2007, 94 facilities released a total of about 7 million pounds of acrylonitrile, most of which (6.6 million pounds) was released by two facilities to on-site hazardous waste underground injection wells (TRI 2009).

Occupational exposure to acrylonitrile may occur during its manufacture and production and in factories where it is used as a monomer; exposure levels are highest where acrylonitrile is manufactured. Typical workplace air concentrations were reported to range from 0.1 to 4 mg/m³ (ATSDR 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 51,153 workers, including 25,320 women, potentially were exposed to acrylonitrile. Occupations with potential for exposure included acrylic resin, rubber, synthetic fiber, and textile maker; synthetic organic chemist; and pesticide worker (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of acrylonitrile on ships and barges.

Department of Transportation (DOT)

Acrylonitrile is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of acrylonitrile is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 20,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.051 µg/L; based on fish or shellfish consumption only = 0.25 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of acrylonitrile = U009, K011, K013.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Acrylonitrile copolymers and resins may be used in materials that are intended for use in producing, manufacturing, processing, preparing, treating, packaging, transporting, or holding food, as prescribed in 21 CFR parts 173, 175, 176, 177, 178, 179, 180, 181.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Ceiling concentration = 10 ppm (15-min exposure).

Permissible exposure limit (PEL) = 2 ppm.

Comprehensive standards for occupational exposure to acrylonitrile have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 10 ppm (15-min exposure).

Immediately dangerous to life and health (IDLH) limit = 85 ppm.

Recommended exposure limit (time-weighted-average workday) = 1 ppm.

Listed as a potential occupational carcinogen.

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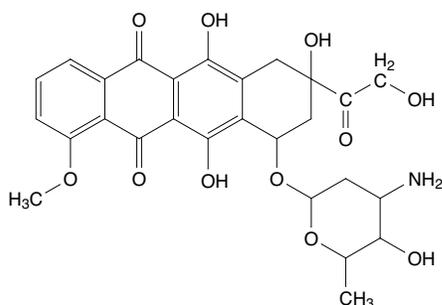
Adriamycin

CAS No. 23214-92-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Adriamycin is a registered trademark of Pharmacia Company for doxorubicin hydrochloride (CAS No. 25136-40-9)



Carcinogenicity

Adriamycin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Adriamycin caused tumors in rats at several different tissue sites and by several different routes of exposure. A single intravenous injection of Adriamycin caused mammary-gland tumors in female rats in several studies. In rats of unspecified sex, single or repeated subcutaneous injections of Adriamycin caused cancer of the mammary gland and at the injection site (sarcoma) (IARC 1976, 1982).

Since Adriamycin was listed in the *Fourth Annual Report on Carcinogens*, additional studies in experimental animals have been identified. In rats of unspecified sex, instillation of Adriamycin into the urinary bladder resulted in a low incidence of benign urinary-bladder tumors (papilloma) and promoted the induction of urinary-bladder tumors by *N*-nitroso-*N*-(4-hydroxybutyl)-*N*-butylamine (IARC 1982, 1987). When Adriamycin was administered to rhesus and cynomolgus monkeys by intravenous injection, a single malignant tumor (fibrosarcoma) was observed at the injection site in one cynomolgus monkey (Thorgeirsson *et al.* 1994, Schoeffner and Thorgeirsson 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to Adriamycin. However, some cancer patients who received Adriamycin in combination with alkylating agents and radiotherapy developed acute non-lymphocytic leukemia and bone tumors (osteosarcoma) (IARC 1982).

Properties

Adriamycin is an anthracycline antibiotic that is an almost odorless red crystalline solid. It is soluble in water and aqueous alcohols, moderately soluble in anhydrous methanol, and insoluble in non-polar organic solvents (IARC 1976). It is stable at room temperature in closed containers under normal storage conditions (Akron 2009). Physical and chemical properties of Adriamycin are listed in the following table.

Property	Information
Molecular weight	543.5 ^a
Melting point	229°C to 231°C ^b
Log K_{ow}	1.27 at pH 7.4 ^a
Water solubility	20 g/L ^a
Vapor pressure	8.99×10^{-25} mm Hg ^b
Dissociation constant (pK_a)	8.33 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Adriamycin is a cytotoxic anthracycline antibiotic used in antimitotic chemotherapy. It is infused intravenously to treat neoplastic diseases such as acute leukemia, multiple myeloma, Hodgkin's disease, non-Hodgkin's lymphoma, soft-tissue and osteogenic sarcomas, Kaposi's sarcoma, neuroblastoma, Ewing's sarcoma, Wilms' tumor, and cancer (carcinoma) of the head and neck, breast, thyroid gland, genitourinary tract, and lung (IARC 1976, Chabner *et al.* 2001, HSDB 2009, MedlinePlus 2009). A liposomal doxorubicin product is available to treat AIDS-related Kaposi's sarcoma.

Production

In 2009, Adriamycin was produced by four manufacturers worldwide (two in Europe and one each in China and East Asia) (SRI 2009); doxorubicin hydrochloride was available from eight U.S. suppliers (ChemSources 2009), and five pharmaceutical companies produced 15 injectable pharmaceutical products approved by the U.S. Food and Drug Administration containing doxorubicin hydrochloride (FDA 2009). No data were found on U.S. imports or exports of Adriamycin.

Exposure

The primary source of human exposure is by intravenous injection of patients treated with Adriamycin. When Adriamycin is used as a single agent for treatment of adult patients, the most common dosage schedule is 60 to 75 mg/m² of body surface as a single intravenous infusion over 30 minutes at 21-day intervals until a total of 550 mg/m² is given (IARC 1976). The liposomal product is also administered intravenously at 21-day intervals at a dose of 20 mg/m² (Chabner *et al.* 2001). In 2009, 378 clinical trials with regimens including Adriamycin were in progress or recently completed (ClinicalTrials 2009). Health-care professionals and support staff (including custodians) may be exposed to Adriamycin by dermal contact, inhalation, or accidental ingestion during drug preparation and administration or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). Adriamycin can be found unchanged in human excrement (RxMed 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 17,132 health-services workers, including 11,918 women, potentially were exposed to Adriamycin (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Adriamycin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Aflatoxins

CAS No. 1402-68-2

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Aflatoxins are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans. Aflatoxins were listed in the *First Annual Report on Carcinogens* as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and limited evidence of carcinogenicity from studies in humans; however, the listing was revised to *known to be human carcinogens* in the *Sixth Annual Report on Carcinogens* in 1991.

Cancer Studies in Humans

Early evidence for the carcinogenicity of aflatoxins in humans came from epidemiological studies (a case-control study and descriptive studies) that correlated geographic variation in aflatoxin content of foods with geographic variation in the incidence of liver cancer

(hepatocellular carcinoma, or primary liver-cell cancer). Studies in Uganda, Swaziland, Thailand, Kenya, Mozambique, and China demonstrated strong, significant positive correlations between estimated aflatoxin intake or aflatoxin levels in food samples and the incidence of liver cancer. In the United States, a 10% excess of primary liver-cell cancer was observed in the Southeast, where the estimated average daily intake of aflatoxin was high, compared with the North and West, areas with low aflatoxin intake. In a case-control study in the Philippines, levels of aflatoxin in the diets of individuals were estimated retrospectively, and the risk of liver cancer increased significantly with increasing estimated aflatoxin consumption. Interpretation of these studies is complicated by potential confounding due to hepatitis B virus infection, which is endemic in many of the study areas and is known to cause primary liver-cell cancer (IARC 1987, 1993).

In studies that took into account the prevalence of chronic hepatitis B infection, aflatoxin exposure remained strongly associated with liver cancer. Chinese studies in which the prevalence of chronic hepatitis B did not appear to fully explain differences in rates of primary liver-cell cancer were reviewed, and it was concluded that the remaining variance in liver-cancer incidence was related both to estimated dietary levels of aflatoxins and to measured levels of aflatoxins and their metabolites in the urine. In a study in Swaziland, estimated aflatoxin intake based on levels in food samples was strongly correlated with liver-cancer incidence; in this study, geographic variation in aflatoxin exposure better explained the variation in liver-cancer incidence than did variation in the prevalence of hepatitis B infection (IARC 1987, 1993).

The International Agency for Research on Cancer concluded in 1987 that there was sufficient evidence in humans for the carcinogenicity of naturally occurring aflatoxins (IARC 1987). This conclusion was reaffirmed in two subsequent reevaluations (IARC 1993, 2002). These reevaluations considered the results of several cohort studies in China and Taiwan, which reported associations between biomarkers for aflatoxin exposure (aflatoxin metabolites in the urine and aflatoxin-albumin adducts in the blood) and primary liver-cell cancer; the association remained when the analyses controlled for hepatitis B infection.

Studies on Mechanisms of Carcinogenesis

Aflatoxin causes genetic damage in bacteria, in cultured cells from humans and experimental animals, and in humans and experimental animals exposed to aflatoxin *in vivo*. Types of genetic damage observed include formation of DNA and albumin adducts, gene mutations, micronucleus formation, sister chromatid exchange, and mitotic recombination. Metabolically activated aflatoxin B₁ specifically induced G to T transversion mutations in bacteria. G to T transversions in codon 249 of the *p53* tumor-suppressor gene have been found in human liver tumors from geographic areas with high risk of aflatoxin exposure and in experimental animals (IARC 1993, 2002).

In humans and susceptible animal species, aflatoxin B₁ is metabolized by cytochrome P450 enzymes to aflatoxin-8,9-epoxide, a reactive form that binds to DNA and to albumin in the blood serum, forming adducts. Comparable levels of the major aflatoxin B₁ adducts (the N⁷-guanine and serum albumin adducts) have been detected in humans and susceptible animal species. The 8,9-epoxide metabolite can be detoxified through conjugation with glutathione, mediated by the enzyme glutathione S-transferase (GST). The activity of GST is much higher (by a factor of 3 to 5) in animal species that are resistant to aflatoxin carcinogenicity, such as mice, than in susceptible animal species, such as rats. Humans have lower GST activity than either mice or rats, suggesting that humans are less capable of detoxifying aflatoxin-8,9-epoxide. In studies of rats and trout, treatment

with chemopreventive agents reduced the formation of aflatoxin B₁-guanine adducts and the incidence of liver tumors.

Cancer Studies in Experimental Animals

Aflatoxins caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Oral administration of aflatoxin mixtures or aflatoxin B₁ alone (in the diet, by stomach tube, or in the drinking water) caused liver tumors (hepatocellular or cholangiocellular tumors) in all species tested except mice; these included rats, hamsters, marmosets, tree shrews, and monkeys. In addition, kidney (renal-cell) and colon tumors occurred in rats, benign lung tumors (adenoma) in mice, and tumors of the liver, bone (osteogenic sarcoma), gallbladder, and pancreas (adenocarcinoma) in monkeys. When administered by intraperitoneal injection, aflatoxin B₁ caused liver tumors in infant mice, adult rats, and toads. Aflatoxin B₁ administered by intraperitoneal injection to pregnant and lactating rats caused tumors of the liver, digestive tract, urogenital system, and nervous system in the mothers and offspring. Aflatoxin mixtures administered by subcutaneous injection caused tumors at the injection site (sarcoma) in rats and mice. Aflatoxins B₂, G₁, and M₁ also caused liver tumors in experimental animals, but generally at lower incidences than did aflatoxin mixtures or aflatoxin B₁ alone. In rats, aflatoxin G₁ also caused kidney tumors when administered orally and a low incidence of injection-site tumors (sarcoma) when administered by intraperitoneal injection. Both enhancement and inhibition of aflatoxin's carcinogenicity were observed following co-administration of aflatoxins with various diets, viruses, parasites, known carcinogens, and other chemicals (IARC 1976, 1993).

IARC (1993) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of naturally occurring mixtures of aflatoxins and aflatoxins B₁, G₁, and M₁; limited evidence for the carcinogenicity of aflatoxin B₂; and inadequate evidence for the carcinogenicity of aflatoxin G₂. In its 2002 evaluation, IARC reported on several more recent studies suggesting that experimental animals infected with hepatitis B virus (woodchucks, tree shrews, and transgenic mice heterozygous for the *p53* tumor-suppressor gene) were more sensitive to the carcinogenic effects of aflatoxin than were uninfected animals. IARC (2002) concluded that these studies confirmed the carcinogenicity of aflatoxins in experimental animals.

Properties

Aflatoxins are toxins produced by fungi in the genus *Aspergillus* that grow on grains and other agricultural crops. They exist as colorless to pale-yellow crystals at room temperature (IARC 1976, 1993). They are slightly soluble in water and hydrocarbons, soluble in methanol, acetone, and chloroform, and insoluble in nonpolar solvents. Aflatoxins are relatively unstable in light and air, particularly in polar solvents or when exposed to oxidizing agents, ultraviolet light, or solutions with a pH below 3 or above 10. Aflatoxins decompose at their melting points, which are between 237°C (G₁) and 299°C (M₁), but are not destroyed under normal cooking conditions. They can be completely destroyed by autoclaving in the presence of ammonia or by treatment with bleach. Physical and chemical properties of aflatoxins are listed in the following table.

Property	Information
Melting point	237°C to 299°C ^a
Log <i>K</i> _{ow}	0.5 ^b
Water solubility	3.150 g/L at 25°C ^b
Vapor pressure	1.25 × 10 ⁻¹⁰ mm Hg at 25°C ^b

Sources: ^aIARC 1993, ^bChemIDplus 2009.

The four major types of aflatoxins are designated aflatoxin B₁ (molecular weight = 312.3), B₂ (molecular weight = 314.3), G₁ (molecular weight = 328.3), and G₂ (molecular weight = 330.3), based on their fluorescent color when exposed to ultraviolet light (B = blue fluorescence, G = yellow-green fluorescence). Aflatoxin M₁, which may be found in the absence of other aflatoxins, is a major metabolic hydroxylation product of aflatoxin B₁.

Use

Aflatoxins are used solely for research purposes. They are naturally occurring contaminants formed by certain fungi on agricultural crops, first discovered in the 1960s (IARC 1976).

Production

Aflatoxins are produced by several fungus species in the genus *Aspergillus*. *A. flavus* and *A. parasiticus* are responsible for most aflatoxin contamination of food crops worldwide. Although these species have similar geographical ranges, *A. parasiticus* is less widely distributed and is rare in Southeast Asia. *A. flavus* is the most widely reported fungus in foodstuffs. *A. australis*, which occurs in the Southern Hemisphere, is the only other species that may be an important source of aflatoxins. Both *A. flavus* and *A. parasiticus* occur in the warm temperate regions of the United States, but are less abundant there than in tropical regions. *A. flavus* is uncommon in cool temperate regions. Both *A. flavus* and *A. parasiticus* produce aflatoxins B₁ and B₂, and *A. parasiticus* also produces aflatoxins G₁ and G₂. The relative proportions and amounts of the various aflatoxins on food crops depend on the *Aspergillus* species present, pest infestation, growing and storage conditions, and other factors. Contamination generally is higher on crops grown in hot, humid tropical climates, but does occur in temperate climates and varies from year to year. Pre-harvest aflatoxin levels increase during droughts, and post-harvest levels increase when crops are not properly dried before storage or are not protected from insect and rodent infestations. Rapid post-harvest drying and storage in an area with a moisture content of less than 10% can eliminate most contamination (IARC 1976, 1993, 2002).

Aflatoxins are not manufactured in commercial quantities but may be produced in small quantities for research purposes. Total annual production was reported to be less than 100 g (IARC 1993, 2002). No U.S. suppliers for aflatoxins were identified in 2009 (ChemSources 2009).

Exposure

The general population is exposed to aflatoxins primarily by eating contaminated food. Aflatoxin-producing fungi commonly grow on corn and other grains, peanuts, tree nuts, and cottonseed meal; however, *A. parasiticus* is rarely found in corn. Meat, eggs, milk, and other edible products from animals that consume aflatoxin-contaminated feed also are sources of potential exposure. Although aflatoxin levels generally are higher during periods of drought, surveys by the U.S. Food and Drug Administration detected aflatoxins in fewer than half of samples collected from feedstuffs even in drought years (Price *et al.* 1993).

Median total aflatoxin concentrations in corn samples collected in the United States between 1978 and 1983 ranged from less than 0.1 to 80 µg/kg (IARC 1993). Data on contamination of foods compiled in 1995 from 90 countries reported a median aflatoxin B₁ concentration of 4 µg/kg (range = 0 to 30 µg/kg) and a median total aflatoxin concentration of 8 µg/kg (range = 0 to 50 µg/kg) (IARC 2002). The estimated daily dietary intake of aflatoxins in the southeastern United States (based on samples collected from 1960 to 1979) was 2.7 ng/kg of body weight, which was substantially less than the daily

intake estimated for periods before 1960 (197 ng/kg for 1910 to 1934 and 108 ng/kg for 1935 to 1959). The time-weighted average daily intake for 1910 to 1979 was 110 ng/kg for the Southeast, but only 0.34 ng/kg for the North and West (Bruce 1990).

Nursing infants may be exposed to aflatoxins in breast milk (Zarba *et al.* 1992). Aflatoxins were detected in 90 of 264 breast-milk samples collected from nursing mothers in Africa, but were not detected in 120 samples collected from nursing mothers in Kiel, Germany. Aflatoxin M₁ was most frequently detected in breast milk, at concentrations varying seasonally from 0.02 to about 1.8 µg/L, but aflatoxin B₁ was found at the highest concentration, 8.2 µg/L (Somogyi and Beck 1993). Biomarkers that may be used to assess aflatoxin exposure include the aflatoxin-DNA adduct in urine and the aflatoxin-albumin adduct in blood serum (Weaver *et al.* 1998).

Occupational exposure to aflatoxins occurs by inhalation of dust generated during the handling and processing of contaminated crops and feeds. Therefore, farmers and other agricultural workers have the greatest risk of occupational exposure. Of 45 animal-feed production plant workers in Denmark, 7 had detectable levels of aflatoxin B₁ in their blood after working for four weeks in the factory or unloading raw materials from ships (Autrup *et al.* 1993). Aflatoxins were detected at concentrations of 0.00002 to 0.0008 µg/m³ in respirable dust samples collected in workplace and storage areas at rice and corn processing plants in India (Ghosh *et al.* 1997). Dust samples collected from 28 U.S. farms during harvest and unloading, animal feeding, and bin cleaning contained aflatoxins at concentrations ranging from 0.00004 to 4.8 µg/m³ (Selim *et al.* 1998). The lowest concentrations were detected during harvest and unloading, and the highest during bin cleaning. Both area and personal samplers were used to determine airborne concentrations of aflatoxins B₁, B₂, G₁, and G₂ in dust samples collected from three food-processing plants (for cocoa, coffee, and spices) in Tuscany, Italy; concentrations ranged from below the level of detection (< 0.000002 µg/m³) to 0.00013 µg/m³ (Brera *et al.* 2002).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Ingredients susceptible to contamination with aflatoxins must comply with FDA rules in the manufacturing and processing of food.

Carbohydrase may be safely used in the production of dextrose from starch, provided that aflatoxin is not present.

Action levels for aflatoxins in foods and animal feed range from 0.5 to 300 ppb.

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Alcoholic Beverage Consumption

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Consumption of alcoholic beverages is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies indicate that the risk of cancer from consumption of alcoholic beverages is most pronounced among smokers and at the highest levels of consumption. Consumption of alcoholic beverages has been shown to cause cancer of the mouth, pharynx, larynx, and esophagus. Cohort and case-control epidemiological studies in a variety of human populations are consistent in reporting moderate to strong associations between alcohol consumption and cancer at these four sites, and the risk of cancer increases with increasing consumption level. The effect of a given level of alcoholic beverage intake on the absolute risk of cancer at these four tissue sites is influenced by other factors, especially smoking. However, smoking does not explain the observed increased risk of cancer associated with increased alcoholic beverage consumption. Evidence also supports a weaker, but possibly causal, relationship between alcoholic beverage consumption and cancer of the liver and breast (IARC 1988, Longnecker 1994, Longnecker and Enger 1996).

Since alcoholic beverage consumption was reviewed for listing in the *Ninth Report on Carcinogens* in 2000, the International Agency for Research on Cancer has reevaluated the evidence for the carcinogenicity of alcoholic beverage consumption (Baan *et al.* 2007, Secretan *et al.* 2009) and concluded that there was sufficient evidence of carcinogenicity in humans. The 2007 and 2009 reviews concluded that alcoholic beverage consumption caused cancer of the mouth, pharynx, larynx, esophagus, liver, colorectum, and female breast.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of alcoholic beverages in experimental animal have been reported. The results of studies specifically examining the carcinogenicity of ethanol in experimental animals do not suggest that the ethanol component of alcoholic bev-

erages is solely responsible for the increased risk of cancer associated with human consumption of alcoholic beverages.

Studies on Mechanisms of Carcinogenesis

The mechanism by which consumption of alcoholic beverages causes cancer in humans has not been established. Increased frequencies of chromosomal aberrations, sister chromatid exchange, and aneuploidy were found in the peripheral-blood lymphocytes of alcoholics. Ethanol-free extracts of some alcoholic beverages caused mutations in bacteria and sister chromatid exchange in cultured human cells (IARC 1988).

Properties

Ethanol and water are the main constituents of most alcoholic beverages. Based on the standard measures for most drinks, the amount of ethanol consumed is similar for beer, wine, and spirits (10 to 14 g). Beer, wine, and spirits also contain volatile and nonvolatile flavor compounds that originate from raw materials, fermentation, wooden casks used for maturation, and synthetic substances added to specially flavored beverages. Although the exact composition of many alcoholic beverages is confidential business information, many studies have identified the organic compounds typically present at low levels. Several of the components and contaminants identified in beer, wine, and spirits are known or suspected human carcinogens, including acetaldehyde, nitrosamines, aflatoxins, ethyl carbamate (urethane), asbestos, and arsenic compounds (IARC 1988).

Use

Alcoholic beverages have been made and used by most societies for thousands of years (IARC 1988). Consumption trends, including overall level of alcohol consumption, beverage choice, age and sex differences, and temporal variations, differ among and within societies. In many cultures, alcohol also has been used in medicine and various pharmaceutical preparations, in religious observances, and in feasting and celebrations.

Production

All alcoholic beverages are produced by the fermentation of fruit or other vegetable matter. Most commercial and home production is of fermented beverages that are classified, based on raw materials and production methods used, as beer, wine, or spirits; smaller quantities of other kinds of fermented beverages (e.g., cider, rice wine, palm wine) also are produced. Beer is produced by fermentation of malted barley or other cereals with the addition of hops. Wine is made from fermented grape juice or crushed grapes; fortified wines include additional distilled spirits. Distilled spirits originate from sources of starch or sugar, including cereals, molasses from sugar beets, grapes, potatoes, cherries, plums, and other fruits; after sugar fermentation, the alcohol content is increased by means of liquid distillation. Although ethanol can be chemically synthesized from ethylene, the alcoholic beverage industry does not synthesize alcohol for use in beverages, because of the presence of impurities from the synthetic process (IARC 1988).

In 1990, the United States produced 4.5 million metric tons (10 billion pounds) of wine, 375 million hectoliters (10 billion gallons) of beer, and 18.5 million hectoliters (490 million gallons) of spirits (ARF 1994). Total world production was 29 million metric tons (6.4 billion pounds) of beer, 1 million hectoliters (26.4 million gallons) of wine, and 58 million hectoliters (1.5 billion gallons) of spirits. In 2008, U.S. per-capita consumption was 21.8 gal of beer, 2.5 gal of wine, and 1.4 gal of distilled spirits (USDA 2010). In 2009, U.S. imports and exports of various categories of beer, wine, distilled spirits,

and other alcoholic beverages ranged from millions to billions of liters (USITC 2009).

Exposure

Alcohol consumption showed a downward trend in the United States and many European countries from the turn of the twentieth century until the period between the two world wars. U.S. alcohol consumption increased from the 1940s until the early 1980s and then began a steady decrease. By 1993, consumption reached the lowest level since 1964; apparent per-capita consumption expressed in gallons of pure alcohol per year was approximately 1.6 gal in 1940, 2.2 gal in 1964, 2.8 gal in 1980, and 2.2 gal in 1993. Most of the decrease in alcohol consumption can be attributed to decreased consumption of spirits. While overall alcohol consumption was falling, per-capita consumption of wine and beer in the United States was relatively stable from the early 1980s into the 1990s (Williams *et al.* 1995). Per-capita consumption of wine was the same in 1993 as in 1977, while consumption of spirits fell by almost 35% over the same period. Per-capita consumption of beer decreased from 1981 to 1985, fluctuated thereafter, and in 1993 was 1% below 1977 consumption levels (NIAAA 1997). The total number of drinks consumed in the United States in 1999 was about 65.5 billion for beer, 13.7 billion for wine, and 29.3 billion for distilled spirits. Underage drinkers (aged 12 to 20) consumed 19.7% of the total, and adult excessive drinkers (more than 2 drinks per day) consumed 46.3%. The heaviest adult drinkers (highest 2.5%) consumed 27% of the total (Foster *et al.* 2003).

Since 1971, the Substance Abuse and Mental Health Services Administration has conducted an annual survey on the use of alcohol, tobacco, and illicit drugs by the civilian noninstitutionalized population of the United States aged 12 years or older (SAMHSA 2009). This survey, now called the National Survey on Drug Use and Health (formerly the National Household Survey on Drug Abuse) reports prevalence and trends of alcohol consumption at three levels: (1) current use (at least one drink in the past 30 days), (2) binge use (five or more drinks on the same occasion at least once in the past 30 days), and (3) heavy use (five or more drinks on the same occasion on at least 5 different days in the past 30 days). In the 2008 survey, 51.6% of respondents reported alcohol use during the past year; this was significantly lower than the 61.9% reported in 2000 and the peak of 72.9% reported in 1979 (Foster *et al.* 2003, SAMHSA 2009). In 2008, 51.6% of respondents (about 129 million) were current drinkers, 23.3% (about 58.1 million) were binge drinkers, and 6.9% (about 17.3 million) were heavy drinkers. Both binge and heavy drinking were most prevalent among young adults (aged 18 to 25). In all age groups except the youngest (aged 12 to 17), men were more likely than women to report drinking alcohol in the past month (SAMHSA 2009).

Regulations

Bureau of Alcohol, Tobacco, Firearms, and Explosives

Alcoholic beverages sold or distributed in the United States, or to members of the Armed Forces outside the United States, must contain a specified health-warning label.

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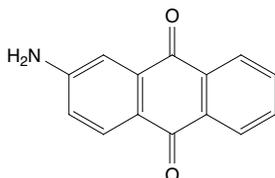
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2-Aminoanthraquinone

CAS No. 117-79-3

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

2-Aminoanthraquinone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-aminoanthraquinone caused tumors in two rodent species and at two different tissue sites. Dietary administration of 2-aminoanthraquinone caused liver cancer (hepatocellular carcinoma) in mice of both sexes and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in male rats. It also caused lymphoma in female mice (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-aminoanthraquinone.

Properties

2-Aminoanthraquinone is an aromatic amine that exists at room temperature as red needle-like crystals or a dark-brown granular solid (NCI 1978). It is practically insoluble in water and diethyl ether, slightly soluble in ethanol, and soluble in chloroform, benzene, and acetone (IARC 1982). It decomposes at its melting point (NCI 1978). Physical and chemical properties of 2-aminoanthraquinone are listed in the following table.

Property	Information
Molecular weight	223.2 ^a
Density	1.45 g/mL ^b
Melting point	302°C ^a
Log K_{ow}	3.31 ^a
Water solubility	0.163 mg/L at 25°C ^a
Vapor pressure	5×10^{-11} mm Hg ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

2-Aminoanthraquinone is used as an intermediate in the industrial synthesis of anthraquinone dyes and pharmaceuticals (HSDB 2009). It is the precursor of 22 dyes and 4 pigments, which include the following: C.I. vat blue 4, 6, 12, and 24, vat yellow 1, and pigment blue 22 (NCI 1978). These dyes are used in automotive paints, high-quality paints and enamels, plastics, rubber, and printing inks, and as textile dyes (HSDB 2009).

Production

2-Aminoanthraquinone was first produced commercially in the United States in 1921 (IARC 1982). In 1965, 520,000 kg (1.1 million pounds) was produced in the United States, but production had decreased to 200,000 lb by 1971 (NCI 1978, IARC 1982). In 2009, 2-aminoanthraquinone was produced by five manufacturers worldwide (three in China, one in Europe, and one in India) (SRI 2009) and was available from 21 suppliers, including 10 U.S. suppliers (ChemSources 2009). In 1974, 360,000 lb of 2-aminoanthraquinone was imported into the United States (NCI 1978), but by 2000, imports had decreased to 1 kg (2.2 lb) (USITC 2009). No other data on U.S. imports or exports of 2-aminoanthraquinone were found.

Exposure

The primary route of potential human exposure to 2-aminoanthraquinone is dermal contact (NCI 1978). Consumers may potentially be exposed to 2-aminoanthraquinone through contact with products containing residues of anthraquinone dyes. Data were not available on the levels of 2-aminoanthraquinone impurities in the final dyes, the potential for consumer exposure, or the potential for human uptake. No environmental releases of 2-aminoanthraquinone were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory. If released to the environment, 2-aminoanthraquinone is expected to exist as a particulate in the atmosphere and to be removed by deposition to water and soil. If released to water, it is expected to adsorb to sediment and not volatilize to the atmosphere. In soil, it is expected to be immobile. It is not expected to biodegrade and has a low potential for bioaccumulation (HSDB 2009).

Because 2-aminoanthraquinone is used on a commercial scale solely by the dye industry, the potential for occupational exposure is greatest for workers at dye-manufacturing facilities. No data were available on the number of facilities using 2-aminoanthraquinone or on the numbers of workers potentially exposed.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act Toxics Release Inventory: Listed substance subject to reporting requirements.

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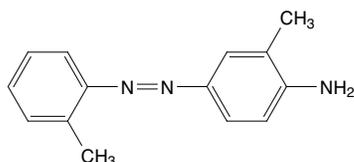
o-Aminoazotoluene

CAS No. 97-56-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as C.I. solvent yellow 3 or fast garnet GBC base



Carcinogenicity

o-Aminoazotoluene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

o-Aminoazotoluene caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Dietary administration of *o*-aminoazotoluene caused benign and/or malignant liver tumors in mice of both sexes (hepatocellular adenoma or carcinoma), male rats (adenoma, hepatocellular carcinoma, cholangioma, or other carcinoma), hamsters of both sexes (hepatocellular adenoma or carcinoma), and dogs of unspecified sex (hepatocellular adenoma or carcinoma, adenocarcinoma, or cholangioma). In mice of both sexes, it also caused lung tumors and benign blood-vessel tumors (hemangioendothelioma in the lung). In addition, urinary-bladder cancer was observed in hamsters of both sexes (papillary or transitional-cell carcinoma) and in dogs of unspecified sex (carcinoma); gallbladder tumors in female hamsters (papilloma or carcinoma) and in dogs of unspecified sex (adenocarcinoma); and mammary-gland cancer (adenocarcinoma) in female hamsters (IARC 1975).

Dermal exposure to *o*-aminoazotoluene caused liver tumors in mice of unspecified sex. Administration of *o*-aminoazotoluene by subcutaneous or intramuscular injection caused hepatocellular liver tumors in female mice, rats of unspecified sex, and newborn mice of both sexes (following a single subcutaneous injection). Also observed were lung tumors in adult and newborn mice of both sexes and cancer at the injection site (fibrosarcoma) in female mice. Administration of *o*-aminoazotoluene by intraperitoneal injection caused hepatocellular liver tumors in mice of both sexes. Benign urinary-bladder tumors (papilloma) following intravesicular instillation in mice and intravesicular implantation in rabbits may also have been exposure-related.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *o*-aminoazotoluene.

Properties

o-Aminoazotoluene is an azo dye that exists at room temperature as odorless reddish-brown to golden crystals or an orange powder. It is practically insoluble in water and soluble in alcohol, ether, chloroform, oils, fats, acetone, cellusolve, and toluene. It remains stable under normal temperatures and pressures (IARC 1975, Akron 2009). Physical and chemical properties of *o*-aminoazotoluene are listed in the following table.

Property	Information
Molecular weight	225.3 ^a
Density	1.21 g/cm ^{3b}
Melting point	101°C to 102°C ^a
Log <i>K</i> _{ow}	3.92 ^a
Water solubility	7.64 mg/L at 25°C ^a
Vapor pressure	7.5 × 10 ⁻⁷ mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

o-Aminoazotoluene is used to color oils, fats, and waxes (IARC 1975). It is also used as a chemical intermediate for the production of the dyes C.I. solvent red 24 and C.I. acid red 115 (HSDB 2009).

Production

Large-scale production of *o*-aminoazotoluene in the United States began in 1914 (IARC 1975). Solvent yellow 3 was manufactured by one U.S. plant in 1979; however, no quantities were reported. In 2009, *o*-aminoazotoluene was produced by one manufacturer in Mexico (SRI 2009) and was available from 19 suppliers worldwide, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of *o*-aminoazotoluene were found.

Exposure

The primary routes of potential human exposure to *o*-aminoazotoluene are dermal contact and inhalation. *o*-Aminoazotoluene is not used directly in foods, drugs, or cosmetics (IARC 1975). The U.S. Environmental Protection Agency's Toxics Release Inventory reported environmental releases of *o*-aminoazotoluene to air in 1988 (250 lb) and 1991 (5 lb) and to surface water in 1990 (5 lb) (TRI 2009). Occupational exposure may occur through inhalation of dust or by dermal contact during production, formulation, or use of *o*-aminoazotoluene (HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,449 workers potentially were exposed to *o*-aminoazotoluene (in the Chemicals and Allied Products and the Transportation Equipment industries); none of these workers were women (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act Toxics Release Inventory: Listed substance subject to reporting requirements.

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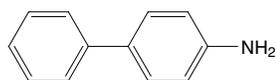
4-Aminobiphenyl

CAS No. 92-67-1

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as para-aminodiphenyl



Carcinogenicity

4-Aminobiphenyl is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Cancer of the urinary bladder was first reported to be associated with occupational exposure to 4-aminobiphenyl in a descriptive epidemiological study (published in the mid 1950s), in which 11% (19 of 171) of workers in a plant manufacturing 4-aminobiphenyl developed urinary-bladder cancer. These workers had been exposed to 4-aminobiphenyl for 1.5 to 19 years between 1935 and 1955. Publication of this study led to an effort to discontinue production and use of 4-aminobiphenyl. Starting in 1955, 541 workers who had been exposed to 4-aminobiphenyl were followed for an additional 14 years; 43 men (7.9%) developed histologically confirmed urinary-bladder cancer. In a survey of workers at a plant producing a variety of chemicals, the risk of mortality from urinary-bladder cancer was elevated tenfold, and all of the men who died of urinary-bladder cancer had worked at the plant during the period when 4-aminobiphenyl was used (1941 through 1952). The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of 4-aminobiphenyl in humans (IARC 1972, 1987).

Since 4-aminobiphenyl was listed in the *First Annual Report on Carcinogens*, most research on its carcinogenicity has focused on exposure from cigarette smoking. Epidemiological studies have reported the incidence of urinary-bladder cancer to be 2 to 10 times as high among cigarette smokers as among nonsmokers. Higher levels of 4-aminobiphenyl adducts (4-aminobiphenyl metabolites bound to DNA or protein) were detected in bladder tumors (DNA adducts) and red blood cells (hemoglobin adducts) from smokers than from nonsmokers (Feng *et al.* 2002). In a case-control study, levels of 4-aminobiphenyl-hemoglobin adducts were higher in smokers with urinary-bladder cancer than in a control group of similarly exposed smokers (Del Santo *et al.* 1991). A Taiwanese study reported that 4-aminobiphenyl-hemoglobin adducts were associated with increased risk of liver cancer (Wang *et al.* 1998).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl from studies in experimental animals. Oral exposure to 4-amino-

biphenyl caused urinary-bladder cancer (carcinoma) in mice, rabbits, and dogs and blood-vessel cancer (angiosarcoma) and liver tumors in mice. 4-Aminobiphenyl administered to rats by subcutaneous injection caused mammary-gland and intestinal tumors (IARC 1987).

Studies on Mechanisms of Carcinogenesis

4-Aminobiphenyl caused genetic damage in several test systems, including mutations in bacteria and in cultured human and other mammalian cells. Other types of genetic damage included mitotic gene conversion in yeast, transformation of cultured mammalian cells, and inhibition of DNA repair in bacteria and cultured mammalian cells. Genetic damage in experimental animals exposed *in vivo* to 4-aminobiphenyl included micronucleus formation, chromosomal aberrations, and sister chromatid exchange (IARC 1987, Shelby *et al.* 1989, Gene-Tox 1998, HSDB 2009).

The mechanism by which 4-aminobiphenyl causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 4-aminobiphenyl, are metabolized, they can be either activated via N-hydroxylation (by cytochrome P450 liver enzymes) or detoxified via pathways such as N-acetylation. The N-hydroxylamine metabolites can form adducts with blood-serum proteins (such as hemoglobin or albumin), which circulate freely, or they can undergo further transformation to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 4-Aminobiphenyl-DNA adducts have been found in urinary-bladder epithelial cells from exposed dogs and humans, and 4-aminobiphenyl-protein adducts have been found in serum albumin from exposed rats and in hemoglobin from humans exposed via cigarette smoking (IARC 1987, Feng *et al.* 2002). Moreover, cigarette smokers who were slow acetylators (with inefficient versions of the enzyme N-acetyltransferase) had higher levels of 4-aminobiphenyl-hemoglobin adducts than did smokers who were rapid acetylators (Vineis 1994).

Properties

4-Aminobiphenyl is an aromatic amine (arylamine) that exists at room temperature as a colorless crystalline solid with a floral odor. It is slightly soluble in cold water, but readily soluble in hot water. It is soluble in ethanol, ether, acetone, chloroform, and lipids. It oxidizes in air and emits toxic fumes when heated to decomposition (Akron 2009). Physical and chemical properties of 4-aminobiphenyl are listed in the following table.

Property	Information
Molecular weight	169.2
Specific gravity	1.16
Melting point	53.5°C
Boiling point	302°C
Log K_{ow}	2.86 at pH 7.5
Water solubility	0.224 g/L at 25°C
Vapor pressure	5.79×10^{-4} mm Hg at 25°C
Vapor density relative to air	5.8
Dissociation constant (pK_a)	4.35 at 18°C

Source: HSDB 2009.

Use

In the United States, 4-aminobiphenyl now is used only in laboratory research. It formerly was used commercially as a rubber antioxidant, as a dye intermediate, and in the detection of sulfates (HSDB 2009).

Production

Because of its carcinogenic effects, 4-aminobiphenyl has not been produced commercially in the United States since the mid 1950s (Koss *et al.* 1969). It was present in the drug and cosmetic color ad-

ditive D&C yellow no. 1; however, use of this color additive was discontinued in the late 1970s (HSDB 2009). 4-Aminobiphenyl has been reported to be formed by the decomposition of 1,3-diphenyltriazene produced by the reaction of diazoaniline and aniline during manufacture of the dye D&C red no. 33 (Bailey 1985). In 2009, 4-aminobiphenyl (for use in research) was available from 11 U.S. suppliers, including one company that supplied bulk quantities (ChemSources 2009). 4-Aminobiphenyl also has been reported as a contaminant in diphenylamine (HSDB 2009).

Exposure

The potential for exposure to 4-aminobiphenyl is low, because it has no commercial uses. Mainstream cigarette smoke was reported to contain 4-aminobiphenyl at levels of 2.4 to 4.6 ng per cigarette (unfiltered) and 0.2 to 23 ng per cigarette (filtered), and sidestream smoke contained up to 140 ng per cigarette (Patrianakos and Hoffmann 1979, Hoffman *et al.* 1997). 4-Aminobiphenyl may be present in the color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 at levels established by the FDA (see Regulations). The concentration of 4-aminobiphenyl in D&C red no. 33 was reported to range from 151 to 856 ppb (mean = 567 ppb) for 10 commercial samples of the dye certified by the FDA in 1983; an eleventh sample contained more than 6,500 ppb 4-aminobiphenyl and was reported to be withdrawn by the manufacturer (Bailey 1985). No data were identified on concentrations of 4-aminobiphenyl in foods prepared with any of the dyes in which 4-aminobiphenyl was permitted, but several studies have reported detectable levels of 4-aminobiphenyl adducts in pancreatic DNA (Ricicki *et al.* 2005) and in hemoglobin (Sarkar *et al.* 2006, Peluso *et al.* 2008) in both smokers and nonsmokers.

The U.S. Environmental Protection Agency's Toxics Release Inventory listed only one facility reporting environmental releases of 4-aminobiphenyl, which ranged from 2 to 48 lb per year from 1988 to 2001, except in 1997 and 1998, when no releases were reported. Most of the releases were to underground injection wells; small amounts were released to air in 1988, 1989, and 2000 (TRI 2009).

At greatest risk for occupational exposure are laboratory technicians and scientists who use 4-aminobiphenyl in research.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

The color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 may contain

4-aminobiphenyl at maximum levels that range from 5 to 275 ppb.

The color additive Ext. D&C yellow no. 1 is banned because of contamination with 4-aminobiphenyl.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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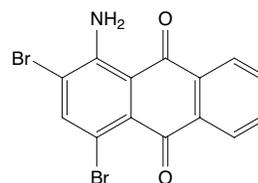
1-Amino-2,4-dibromoanthraquinone

CAS No. 81-49-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as ADBAQ



Carcinogenicity

1-Amino-2,4-dibromoanthraquinone (ADBAQ) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to ADBAQ caused tumors at several different tissue sites in rats and mice. ADBAQ administered in the diet caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats and mice of both sexes. In rats of both sexes, it also caused cancer of the large intestine (carcinoma) and urinary bladder (transitional-cell carcinoma) and increased the combined frequency of benign and malignant kidney tumors (renal-tubule adenoma and carcinoma). In mice of both sexes, it also caused cancer of the forestomach (squamous-cell carcinoma) and increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) (NTP 1996).

Cancer Studies in Humans

Two epidemiological cohort studies evaluated the risk of cancer among workers in plants manufacturing anthraquinone dyes; however, it is not known whether workers were exposed specifically to ADBAQ (Gardiner *et al.* 1982, Delzell *et al.* 1989). Some evidence suggests that anthraquinone-dye workers may have an increased risk of cancer. Significant excesses of esophageal and prostate cancer occurred among workers in some areas of an anthraquinone-dyestuffs plant in Scotland, and excesses of lung and central-nervous-system cancer occurred among workers at a New Jersey anthraquinone dye and epichlorohydrin plant (Barbone *et al.* 1992, 1994, Sathiakumar and Delzell 2000). Nevertheless, estimates of risk in all studies were based on small numbers of cancer deaths, and workers may have been exposed to other carcinogens.

Studies on Mechanisms of Carcinogenesis

ADBAQ is rapidly absorbed from the gastrointestinal tract and distributed to most soft tissues. The majority of ADBAQ is metabolized, and both ADBAQ and its metabolites are excreted in the feces and urine. However, the metabolites of ADBAQ have not been identified (NTP 1996). Evaluation of ADBAQ's genetic effects has been hindered by its limited solubility. ADBAQ caused mutations in some strains of bacteria but not in cultured rodent cells, which were tested at lower concentrations (Haworth *et al.* 1983, NTP 1996). In cultured mammalian cells, ADBAQ caused chromosomal aberrations and sister chromatid exchange; however, the results varied among laboratories and among trials at the same laboratory (Loveday *et al.* 1990, NTP 1996). Point mutations in the *ras* proto-oncogene occurred at a higher frequency in forestomach and lung tumors from the two-year carcinogenicity study of ADBAQ-exposed mice than in spontaneous tumors from control mice not exposed to ADBAQ. The predominant types of mutations were A to T transversions and A to G transitions, suggesting that ADBAQ or its metabolites target adenine bases in the *ras* proto-oncogene (Hayashi *et al.* 2001).

The mechanism by which ADBAQ causes cancer is not known. Four other anthraquinones (2-aminoanthraquinone, 1-amino-2-methylanthraquinone, danthron [1,8-dihydroxyanthraquinone], and disperse blue 1 [1,4,5,8-tetraaminoanthraquinone]) are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. There is no evidence to suggest that mechanisms by which ADBAQ causes tumors in experimental animals would not also operate in humans.

Properties

ADBAQ is an anthraquinone-derived vat dye that is a reddish-brown to orange powder at room temperature (NTP 1996). It is insoluble in water, making it a colorfast dye. Physical and chemical properties of ADBAQ are listed in the following table.

Property	Information
Molecular weight	381 ^a
Melting point	221°C ^a
Log K_{ow}	5.31 ^b
Water solubility	0.000015 g/L at 25°C ^b
Vapor pressure	1.44×10^{-7} mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

ADBAQ and other aminoanthraquinones are key intermediates in the production of almost all anthraquinone dyes (HSDB 2009). Anthraquinones, including ADBAQ, are widely used as starting material for the manufacture of vat dyes, which are a class of water-insoluble dyes that can easily be reduced to a water-soluble and usually colorless form. In this form, they are readily impregnated into fibers and textiles. Oxidation then produces an insoluble colored form that is remarkably fast to washing, light, and chemicals. Vat dyes typically are used with cotton, wool, and cellulose acetate (NTP 1996).

Production

ADBAQ is prepared from 1-aminoanthraquinone by bromination in dilute mineral acids (HSDB 2009). In 2009, ADBAQ was produced by one manufacturer in China and was available from at least five U.S. suppliers (SRI 2009, ChemSources 2009). In 1991, U.S. production of all vat dyes totaled 14 million kilograms (31 million pounds) (NTP 1996).

Exposure

The primary route of potential exposure to ADBAQ is through dermal contact. Because ADBAQ has a very low vapor pressure, inhalation exposure to vapor is unlikely; however, contaminated dust particles could be inhaled. ADBAQ is not known to be formed naturally in the environment, but may be released into the environment during its production or through its use in the production of anthraquinone dyes. ADBAQ was detected in raw wastewater of a dye manufacturing plant in four of eight samples, at concentrations of 92 to 170 ppb. However, it was not detected in the final effluent before its release into a nearby river or in sediments from the river, which suggests that ADBAQ may have been biodegraded or adsorbed to sludge during wastewater treatment (HSDB 2009). No information was found on occupational exposure specifically to ADBAQ or to anthraquinone dyes in general; however, epidemiological studies indicated occupational exposure to anthraquinone dyes in a New Jersey dye and resin manufacturing plant (Sathiakumar and Delzell 2000).

Regulations

No regulations or guidelines relevant to reduction of exposure specifically to ADBAQ were identified.

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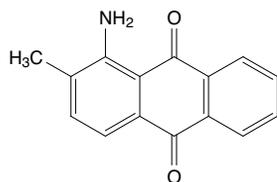
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1-Amino-2-methylantraquinone

CAS No. 82-28-0

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

1-Amino-2-methylantraquinone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1-amino-2-methylantraquinone caused tumors in two rodent species and at two different tissue sites. Dietary administration of technical-grade 1-amino-2-methylantraquinone increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice. In rats, it caused liver cancer in both sexes and increased the combined incidence of benign and malignant kidney tumors (tubular-cell adenoma and carcinoma and adenocarcinoma) in males (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1-amino-2-methylantraquinone.

Properties

1-Amino-2-methylantraquinone is an anthraquinone dye and dye intermediate that exists as an orange solid at room temperature (NCI 1978). It is practically insoluble in water; soluble in acetone, benzene, ethanol, ethylene glycol, monoethyl ether, and linseed oil; and slightly soluble in carbon tetrachloride (IARC 1982, ChemIDplus 2009). Phys-

ical and chemical properties of 1-amino-2-methylantraquinone are listed in the following table.

Property	Information
Molecular weight	237.3 ^a
Melting point	206°C ^a
Log <i>K</i> _{ow}	4.07 ^b
Water solubility	0.332 mg/L at 25°C ^b
Vapor pressure	3.82 × 10 ⁻⁸ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

1-Amino-2-methylantraquinone was used almost exclusively as a dye and as an intermediate in the production of dyes. It was used as a dye for synthetic fibers, furs, and thermoplastic resins. The only dyes derived from 1-amino-2-methylantraquinone that were produced in the United States were C.I. acid blue 47, last produced in 1973, and C.I. solvent blue 13, last produced in 1974 (IARC 1982, HSDB 2009).

Production

U.S. production of 1-amino-2-methylantraquinone began in 1948 and ended in 1974 (IARC 1982). In 2009, 1-amino-2-methylantraquinone was produced by one manufacturer in Europe (SRI 2009) and was available from twelve suppliers, including three U.S. suppliers (ChemSources 2009). U.S. imports of 1-amino-2-methylantraquinone were last reported in 1972, when 120 kg (265 lb) was imported (IARC 1982).

Exposure

The primary routes of potential human exposure to 1-amino-2-methylantraquinone are inhalation and dermal contact. The potential for exposure is limited, because 1-amino-2-methylantraquinone is no longer produced commercially in the United States or reported to be imported. No data were found on environmental releases of 1-amino-2-methylantraquinone. The potential for occupational exposure was greatest among workers engaged in textile dyeing; however, no data were found on the numbers of workers potentially exposed (HSDB 2009).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

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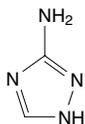
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Amitrole

CAS No. 61-82-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Amitrole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Amitrole caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) and liver tumors (hepatocellular tumors) when administered to rats of both sexes in the feed or drinking water and to 7-day-old weanling mice of both sexes by stomach tube for three weeks and in the diet starting at four weeks of age. It also caused liver and thyroid-gland tumors in rats (of unspecified sex) when administered by subcutaneous injection (IARC 1974, Tsuda *et al.* 1976).

Since amitrole was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of amitrole caused cancer of the thyroid gland (follicular-cell carcinoma) in rats of both sexes and marginally increased the incidence of benign pituitary-gland tumors (adenoma) in female rats (IARC 1986, 1987, 2001). Dietary administration of amitrole to female mice nursing pups and then to the weaned offspring caused liver cancer (hepatocellular carcinoma) in the male offspring (IARC 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to amitrole. A small cohort study of Swedish railroad workers who had sprayed herbicides found a statistically significant excess of all cancers among those exposed to both amitrole and chlorophenoxy herbicides, but not among those exposed mainly to amitrole (IARC 1974).

Properties

Amitrole is a triazole compound that is a colorless to white crystalline solid at room temperature (Akron 2009, HSDB 2009). It forms salts with most acids and bases and is a powerful chelating agent (IPCS 1994). It is soluble in water, ethanol, methanol, chloroform, and acetonitrile; sparingly soluble in ethyl acetate; and insoluble in acetone (HSDB 2009). Amitrole is stable under normal temperatures and pressures, but decomposes on exposure to light (Akron 2009). Physical and chemical properties of amitrole are listed in the following table.

Property	Information
Molecular weight	84.1 ^a
Specific gravity	1.14 mg/mL at 20°C ^a
Melting point	159°C ^a
Log K_{ow}	-0.97 ^a
Water solubility	280 g/L at 25°C ^a
Vapor pressure	4.4×10^{-7} mm Hg at 25°C ^a
Dissociation constant (pK_a)	4.2 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Amitrole was first registered for use as an herbicide in the United States in 1948 but was not commercialized until the 1950s (EPA 1996). In 1958, food-crop use was limited to post-harvest application to cranberries (EPA 1996, IARC 2001). Registrations for use on food crops were cancelled by the U.S. Environmental Protection Agency in 1971, after which amitrole was used primarily as a non-selective terrestrial post-emergent herbicide in outdoor industrial areas, non-agricultural rights of way, and non-agricultural uncultivated areas to treat vines, shade trees, ornamental shrubs and trees, and soil. Amitrole has a wide spectrum of activity against annual and perennial broad-leaf and grass-type weeds. Approved uses on soil were for non-crop land prior to sowing and for inter-row weed control in tree and vine crops, where contact with food plants was avoided (IPCS 1994). Limitations on the use of amitrole included not feeding or grazing animals on land treated with amitrole and not applying it directly to water or wetlands. Amitrole was usually applied by fixed-boom sprayers attached to tractors, trucks, or railroad wagons (EPA 1996, IARC 2001).

Production

Amitrole was first synthesized in 1898 (IARC 2001). At one time, 40 registered pesticide products contained amitrole as an active ingredient; however, no active registered products in the United States now contain amitrole (EPA 2009). Amitrole was not reported to be produced commercially in the United States in surveys conducted in 1978 and 1982 (HSDB 2009). In 2009, amitrole was produced by one manufacturer in Europe and two manufacturers in East Asia (SRI 2009) and was available from 34 suppliers, including 23 U.S. suppliers (ChemSources 2009). Reported U.S. imports of amitrole were 1.2 million pounds in 1978, but had declined to 465,000 lb by 1982 (HSDB 2009). No data on U.S. imports or exports after 1985 were found. A report filed in 1990 under EPA's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of amitrole totaled 10,000 to 500,000 lb (EPA 2004); no inventory update reports were filed for amitrole in 1994, 1998, or 2002.

Exposure

The routes of potential human exposure to amitrole are inhalation, dermal contact, and ingestion (HSDB, 2009). Exposure of the general population could occur through ingestion of contaminated drinking water. Because amitrole is not registered for food-crop uses, there is no known dietary exposure. In 1958 and 1959, amitrole residues were found on cranberries (EPA 1996, HSDB 2009). No amitrole residues were detected in food or water when recommended use practices were followed (IPCS 1994). Exposure could previously have occurred through inhalation near herbicide manufacturing or spraying areas. Large quantities of amitrole previously were used as an herbicide in the United States. In California alone, 82,000 kg (180,000 lb) was used in 1970 and 64,000 kg (141,000 lb) was used in 1972 (IARC 1974). EPA estimated that annual use was 500,000 to 800,000 lb in 1984, declining to between 50,000 and 100,000 lb in 1989 and between 40,000 and 60,000 lb in 1990 (EPA 1996). One death from ingestion of a weed killer containing a mixture of amitrole and ammonium thiocyanate was reported; amitrole was measured in the blood of the victim at 13 mg/L over 12 hours after ingestion (Legras *et al.* 1996).

According to EPA's Toxics Release Inventory, 176 lb of amitrole was released to the environment in 1999, mostly to off-site facilities, and slightly over 100 lb was released in 2007, to off-site facilities. The largest total annual releases were of 265 lb to off-site landfills in 2001 (TRI 2009). When amitrole is released to air, it reacts with photochemically produced hydroxyl radicals, with a half-life of 3 days (EPA

1996, HSDB 2009). It was measured in the air near a manufacturing facility at concentrations as high as 100 µg/m³ (IPCS 1994). In water and soil, amitrole is not expected to hydrolyze, but it is readily biodegraded by soil microorganisms; it is not likely to bioaccumulate in aquatic organisms. Amitrole is moderately persistent under aerobic conditions, with half-lives of 57 days in water and 22 to 26 days in soil, but it is more persistent under anaerobic conditions, with a half-life of over 1 year in water (EPA 1996, HSDB 2009). Amitrole is highly mobile in alkaline or neutral soils and leaches into groundwater, but it can be bound moderately by cation-exchange reactions in acidic soils, resulting in moderate mobility (EPA 1996, IPCS 1994). Concentrations of amitrole in a river downstream from a production plant ranged from 0.5 to 2 mg/L (IPCS 1994). When amitrole was sprayed on a watershed in Oregon for control of weeds, it was detected in the stream 30 minutes after the aerial spray application at a concentration of 155 µg/L, but not after 6 days (detection limit = 2 µg/L) (Marston *et al.* 1968).

Occupational exposure to amitrole could have occurred during its manufacture, packaging, or application as a herbicide. Particulates containing amitrole could have been released during its production (IPCS 1994). Those most likely to have been exposed were pesticide mixers, loaders, and applicators (EPA 1996). In Sweden, railroad workers exposed during spraying of track areas reported both inhalation exposure and dermal exposure due to wet spray on the hands and face (Axelson *et al.* 1980). According to the National Occupational Exposure Survey (conducted from 1981 to 1983), 693 workers potentially were exposed to amitrole, including 24 women (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of amitrole = U011.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.2 mg/m³.

Listed as a potential occupational carcinogen.

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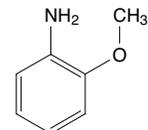
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o-Anisidine and Its Hydrochloride

CAS Nos. 90-04-0 and 134-29-2

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

o-Anisidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *o*-anisidine administered as its hydrochloride salt caused tumors in two rodent species and at two different tissue sites. Dietary administration of *o*-anisidine hydrochloride increased the combined incidence of benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) in rats and mice of both species. In male rats, it also caused kidney cancer (transitional-cell carcinoma of the renal pelvis) and increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma, papillary cystadenoma, and cystadenocarcinoma) (NCI 1978, IARC 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *o*-anisidine or *o*-anisidine hydrochloride.

Properties

o-Anisidine is an aromatic amine that exists at room temperature as a liquid with an amine-like odor and ranging in color from colorless to yellowish, pink, or reddish. It is soluble in water, miscible with etha-

nol, benzene, diethyl ether, and acetone, and soluble in dilute mineral acids. *o*-Anisidine hydrochloride is a salt of *o*-anisidine. It is a gray-black crystalline solid or light gray powder at room temperature and is soluble in water (HSDB 2009). Physical and chemical properties of *o*-anisidine and its hydrochloride salt are listed in the following table.

Property	<i>o</i> -Anisidine	<i>o</i> -Anisidine HCl
Molecular weight	123.2	159.6
Specific gravity	1.10 at 15°C/15°C	NR
Melting point	5°C	225°C
Boiling point	225°C	NR
Log K_{ow}	1.18	NR
Water solubility	14 g/L at 25°C	soluble
Vapor pressure	0.08 mm Hg at 25°C	0.414 mm Hg at 25°C
Vapor density relative to air	4.25	6.77
Dissociation constant (pK _a)	4.53	NR

Source: HSDB 2009. NR = not reported.

Use

o-Anisidine hydrochloride is used as a chemical intermediate in the production of numerous azo and triphenylmethane dyes and pigments (e.g., C.I. direct red 72, disperse orange 29, direct yellow 44, direct red 24, and acid red 4); in the production of pharmaceuticals, including the expectorant guaiaicol; as a corrosion inhibitor for steel; and as an antioxidant for polymercaptan resins (IARC 1999, HSDB 2009).

Production

o-Anisidine was produced commercially in the United States from the 1920s until 1957 (IARC 1982). In 2009, six manufacturers of *o*-anisidine were identified worldwide, but none for the hydrochloride salt (SRI 2009). *o*-Anisidine was available from 44 suppliers, including 20 U.S. suppliers, and the hydrochloride salt was available from 8 suppliers, including 5 U.S. suppliers (ChemSources 2009). U.S. imports of *o*-anisidine and its hydrochloride salt are reported in the category "*o*-anisidines, *p*-anisidines, and *p*-phenetidine," and U.S. exports are reported in the category "anisidines, dianisidines, phenetidines and their salts." From 1989 to 2008, imports in the category ranged from a high of over 4.6 million kilograms (10.1 million pounds) in 1996 to zero in 2007 and 2008, and exports ranged from zero to 262,000 kg (577,000 lb) (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *o*-anisidine totaled 500,000 lb to 1 million pounds in 1986, 1990, and 2006; 1 million to 10 million pounds in 1990 and 1998; and 10,000 to 500,000 lb in 2002 (EPA 2004, 2009).

Exposure

The primary routes of potential human exposure to *o*-anisidine and *o*-anisidine hydrochloride are inhalation and dermal contact; exposure may also occur by ingestion (HSDB 2009). Individuals in the population could be exposed to *o*-anisidine in the environment. *o*-Anisidine occurs in cigarette smoke and as an environmental pollutant in wastewater from oil refineries and chemical plants (IARC 1982, 1999). Mean concentrations of *o*-anisidine in smoke from market, reference, and other cigarettes were reported to range from less than 0.2 to 5.12 ng per cigarette (Stabbert *et al.* (2003). *o*-Anisidine was detected at concentrations ranging from less than 0.05 to 4.2 µg/L (median = 0.22 µg/L) in urine samples from 20 members of the general population in Germany (Weiss and Angerer 2002). Hemoglobin adducts of *o*-anisidine were detected in all blood samples from 224 children in three German cities; however, adduct levels did not dif-

fer significantly between children exposed to environmental tobacco smoke and unexposed children (Richter *et al.* 2001).

According to EPA's Toxics Release Inventory, environmental releases of *o*-anisidine between 1988 and 1992 peaked in 1989, when 10,000 lb was released, including almost 5,000 lb to surface water. During this period, most releases were to air; however, 250 lb was released to landfills annually from 1989 through 1992, and 2,000 to 3,600 lb to surface impoundments in 1989, 1991, and 1992. From 1993 to 2007, releases were much lower and remained fairly steady; in 2007, releases totaled 638 lb. Releases of hydrochloride salt have not been reported (TRI 2009). If released to air, *o*-anisidine is expected to remain in the vapor phase and to be degraded by reaction with hydroxyl radicals, with a half-life of 6 hours. If released to surface water, it is expected to bind to sediment or suspended solids with high organic matter content and to volatilize from water with an estimated half-life of 31 days from streams and 350 days from lakes. *o*-Anisidine has little potential to bioaccumulate in aquatic organisms. If released to soil, it will likely bind to humic materials; at low concentrations, it will be subject to rapid biodegradation under aerobic conditions (HSDB 2009).

Occupational exposure to *o*-anisidine and its hydrochloride salt may occur during their production and use as a chemical intermediate, corrosion inhibitor, or antioxidant (IARC 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 705 workers in the Chemicals and Allied Products industry potentially were exposed to *o*-anisidine and 1,108 workers in the same industry potentially were exposed to *o*-anisidine hydrochloride (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: *o*-Anisidine is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.5 mg/m³ for *o*-anisidine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m³ for *o*-anisidine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 mg/m³ for *o*-anisidine.

Recommended exposure limit (REL) = 0.5 mg/m³ for *o*-anisidine.

o-Anisidine is listed as a potential occupational carcinogen.

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Aristolochic Acids

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Twelfth Report on Carcinogens* (2011)

Carcinogenicity

Aristolochic acids are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis. Evidence of carcinogenicity from studies in experimental animals supports the findings in humans.

Cancer Studies in Humans

The evidence for carcinogenicity in humans is based on (1) findings of high rates of urothelial cancer, primarily of the upper urinary tract, among individuals with renal disease who had consumed botanical products containing aristolochic acids and (2) mechanistic studies in humans which demonstrate that aristolochic acids are the carcinogenic agents in these products.

Evidence for the carcinogenicity of aristolochic acids was first identified in studies of Belgian patients with nephropathy (progressive interstitial renal fibrosis) related to the consumption of herbal medicines. The patients had consumed Chinese herbal medicines that were inadvertently contaminated with plant species of the genus *Aristolochia*. Aristolochic acids were considered to be the cause of the nephropathy (now referred to as "aristolochic acid nephropathy," or AAN) because (1) the nephropathy developed immediately after ingestion of the herbs, (2) in most cases, the patients had not been exposed to other agents known to be risk factors for nephropathy, (3) aristolochic acids were identified in the herbal products, and (4) aristolochic acid metabolites bound to DNA (AA-DNA adducts) were found in tissues (usually kidney or urothelial tissue) from some of the patients. Over 100 cases of AAN have been reported in Belgium and over 170 cases in other locations, including the United States, Great Britain, Japan, Taiwan, and China (Arlt *et al.* 2002, NTP 2008).

Two prevalence studies in Belgium (at Cliniques Universitaires St.-Luc and Hospital Erasme) reported high rates of urothelial cancer (40% to 46%), mainly of the upper urinary tract, among female AAN patients who had received kidney transplants (Cosyns *et al.* 1999, Nortier *et al.* 2000, Nortier and Vanherweghem 2002). This rate of urothelial cancer among AAN patients is much higher than the incidence or prevalence of transitional-cell carcinoma of the urinary tract (i.e., urothelial carcinoma) (0.89% to 4%) reported in several studies

of Chinese patients with renal disease, either renal-transplant patients or dialysis patients (Ou *et al.* 2000, Wu *et al.* 2004, and Li *et al.* 2008). Neither prevalence study had an unexposed comparison group. Both studies identified aristolochic acids in the botanical products consumed by the patients, and both studies detected AA-DNA adducts in kidney tissue from the patients, demonstrating that the patients had been exposed to aristolochic acids. In the study at Hospital Erasme, the rate of urothelial cancer was significantly higher among AAN patients who had consumed a high dose of the plant *Aristolochia fangchi* than among patients who had consumed a lower dose. Furthermore, AAN patients with and without urothelial cancer did not differ significantly with respect to other risk factors for urothelial cancer, such as smoking or the use of analgesics or nonsteroidal anti-inflammatory drugs. A 15-year follow-up study of AAN patients from Hospital Erasme found a rate of upper-urinary-tract urothelial cancer similar to that previously reported by Nortier and colleagues (Lemy *et al.* 2008). In addition, AAN patients with upper-urinary-tract urothelial cancer had an unusually high incidence of urinary-bladder urothelial cancer.

Additional case reports and clinical investigations of urothelial cancer in AAN patients outside of Belgium support the conclusion that aristolochic acids are carcinogenic (NTP 2008). The clinical studies found significantly increased risks of transitional-cell carcinoma of the urinary bladder and upper urinary tract among Chinese renal-transplant or dialysis patients who had consumed Chinese herbs or drugs containing aristolochic acids, using non-exposed patients as the reference population (Li *et al.* 2005, 2008).

Molecular studies suggest that exposure to aristolochic acids is also a risk factor for Balkan endemic nephropathy (BEN) and upper-urinary-tract urothelial cancer associated with BEN (Grollman *et al.* 2007). BEN is a chronic tubulointerstitial disease of the kidney, endemic to Serbia, Bosnia, Croatia, Bulgaria, and Romania, that has morphology and clinical features similar to those of AAN. It has been suggested that exposure to aristolochic acids results from consumption of wheat contaminated with seeds of *Aristolochia clematitis* (Ivic 1970, Hranjec *et al.* 2005, NTP 2008). AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Furthermore, A:T to T:A transversion mutations in the *p53* tumor-suppressor gene were found in urothelial tumors from BEN patients (Grollman *et al.* 2007).

The available studies are limited in their ability to formally address confounding by other factors that could increase the risk of cancer, and the case-series studies did not include unexposed controls; however, a causal association between exposure to aristolochic acids and human cancer is evidenced by the strength of the association, consistency across studies, dose-response effects, detection of AA-DNA adducts in exposed patients, timing of the exposure and disease, and specific mutations in the *p53* gene similar to the A:T to T:A transversions seen in rodents and rodent cell cultures exposed to aristolochic acids. The finding of urothelial cancer among patients who consumed a variety of botanical products from different plant species known to contain aristolochic acids provides additional support for the role of aristolochic acids as the cancer-causing agent in the botanical products. In 2000, the International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of herbal remedies containing plant species of the genus *Aristolochia* in humans (IARC 2002). In 2008, IARC concluded that aristolochic acids also were carcinogenic to humans (Grosse *et al.* 2009).

Studies on Mechanisms of Carcinogenicity

Aristolochic acids are absorbed after oral exposure; no data are available on absorption after dermal or inhalation exposure (NTP 2008). Aristolochic acids I and II (AAs I and II) are the most widely studied aristolochic acids. Aristolochic acids are metabolized to aristolactams, which are further metabolized to a cyclic *N*-acylnitrenium ion, a reactive intermediate that forms adducts with purine bases (adenine and guanine) in DNA (dA-AAI, dG-AAI, dA-AAII, and dG-AAII). A number of cytosolic and microsomal enzymes (CYP1A1, CYP1A2, NADPH:CYP reductase, prostaglandin H synthase, DT-diaphorase, xanthine oxidase, cyclooxygenase, and NAD(P)H:quinone oxidoreductase) are capable of bioactivating aristolochic acids to the reactive form (NTP 2008).

DNA adducts have been detected *in vitro* in experimental animals exposed to aristolochic acids and in human tissue from individuals exposed to aristolochic acids, including individuals with AAN, BEN, or urothelial cancer associated with AAN or BEN (Grollman *et al.* 2007, NTP 2008). In animals, adducts have been detected in the forestomach and stomach, urinary tract (kidney and urinary bladder), liver, intestine, spleen, and lung. In humans, adducts have been detected in the urinary tract (kidney, ureter, and urinary bladder), liver, and non-target tissues such as pancreas, breast, and lung (NTP 2008). The predominant adduct, dA-AAI, persists for a lifetime in rats and at least 89 months in humans and appears to be responsible for most of the mutagenic and carcinogenic properties of aristolochic acids (NTP 2008).

Aristolochic acids (purified I or II or mixtures) have been shown to be mutagenic in bacteria, cultured cells, and rodents exposed *in vivo*. AA I has been tested the most extensively. In *in vitro* assays, purified aristolochic acids induced mutations in the bacterium *Salmonella typhimurium* and in cultured mammalian cells, including (1) *hprt* mutations in rat fibroblast-like cells and Chinese hamster ovary cells, (2) forward mutations in mouse lymphoma cells, and (3) mutations in the *p53* DNA-binding domain in two studies with fibroblast cell cultures from human *p53* knock-in (Hupki) mice (mice carrying a humanized *p53* gene sequence) (NTP 2008). Mutations were identified in the *p53* DNA-binding domain in one third (6 of 18) to half (5 of 10) of the established Hupki mouse fibroblast cultures; A:T to T:A transversions were predominant, occurring in at least 80% of the cell lines with mutations (Liu *et al.* 2004). Aristolochic acid mixtures or plant extracts caused mutations in *S. typhimurium* and sex-linked recessive lethal mutations in the fruit fly *Drosophila melanogaster* (NTP 2008). In studies with rodents exposed *in vivo*, exposure to aristolochic acid mixtures or plant extracts caused (1) mutations in subcutaneous granulation tissue from Sprague-Dawley rats (Maier *et al.* 1985), (2) mutations of the *lacZ* transgene in forestomach, kidney, and colon tissue from transgenic Muta mice (Kohara *et al.* 2002), and (3) mutations of the *cII* transgene in liver and kidney tissue from transgenic Big Blue rats (Chen *et al.* 2006, Mei *et al.* 2006). A:T to T:A transversions were the predominant mutation type in the Muta mice and Big Blue rats. Exposure to AA I also caused mutations in granulation tissue from Sprague-Dawley rats (Maier *et al.* 1987).

Aristolochic acids have been shown to bind to adenine in codon 61 in the *H-ras* mouse oncogene and to purines in the human *p53* gene. Mutations identified in tumors of rodents exposed to aristolochic acids include A:T to T:A transversions in codon 61 of the *c-Ha-ras* gene in forestomach tumors (from rats and mice), lung tumors (from rats and mice), and ear-duct tumors (from rats). No mutations were identified in tissues from rats with chronic renal failure that had not been exposed to aristolochic acids (Schmeiser *et al.* 1990, 1991). Similar findings have been reported in humans. A:T to T:A transversion mutations of the *p53* gene were identified in a urothelial tumor

from an AAN patient (Lord *et al.* 2004) and at a high frequency (78%) in BEN patients with upper-urinary-tract urothelial cancer. The frequency of A:T to T:A transversions of *p53* mutations in bladder and ureter tumors not caused by aristolochic acid exposure was approximately 5% (Grollman *et al.* 2007). Moreover there was concordance between the location of the *p53* A to T transversions and mutations identified in fibroblast cell cultures from human *p53* knock-in (Hupki) mice treated with AA I (Nedelko *et al.* 2008).

Aristolochic acids also caused other types of genetic damage in other test systems with and without mammalian metabolic activation. Aristolochic acids I and II and mixtures caused DNA damage in the SOS chromotest in the bacterium *Escherichia coli*, and aristolochic acid mixtures caused sex-chromosome loss and somatic recombination in *D. melanogaster*. In mammalian cells exposed *in vitro*, aristolochic acid mixtures caused chromosomal aberrations, sister chromatid exchange, and micronucleus formation in human lymphocytes. AA I also caused chromosomal aberrations and sister chromatid exchange in Chinese hamster ovary cells. Neither AA I nor AA II induced DNA strand breaks in rat liver cells, but aristolochic acids caused DNA damage in a pig kidney cell line (proximal tubular epithelial cells) and in human hepatocellular carcinoma cells. In mammalian *in vivo* studies, aristolochic acids (composition not specified) did not induce unscheduled DNA synthesis in the pyloric mucosa of male rats. DNA damage was reported in kidney cells isolated from male Sprague-Dawley rats administered a single oral dose of an aristolochic acid mixture. One study reported that intravenous injection of aristolochic acid mixtures increased micronucleus formation in polychromatic erythrocytes in bone marrow from NMRI male and female mice, but another study found no increase in micronucleus formation in peripheral blood reticulocytes from male Muta mice exposed orally to a mixture of AAs I and II (NTP 2008).

Together, these findings strongly suggest that exposure to aristolochic acids causes urothelial cancer in humans through formation of DNA adducts (specifically, through binding of the reactive metabolite with adenine) and the resulting transversion mutations in oncogenes.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of aristolochic acids in experimental animals based on studies showing that aristolochic acids caused tumors in rodents and rabbits at several different tissue sites and by several different routes of exposure. Although the studies in which aristolochic acids were administered orally or by injection typically were small and of short duration, they showed clear evidence of carcinogenicity. In nearly all of the studies, aristolochic acids caused urothelial tumors, as they did in humans.

Oral exposure to aristolochic acids caused predominantly forestomach and urinary-tract tumors, and administration by injection caused mainly urinary-tract tumors and connective-tissue tumors (sarcoma) at the injection site (NTP 2008). In female mice, oral exposure to aristolochic acids caused tumors of the forestomach, stomach, kidney, lung, and uterus and malignant lymphoma (Mengs 1988). In several studies in rats, oral exposure to aristolochic acids caused tumors of the forestomach, kidney (renal-cell and renal-pelvis tumors), urinary bladder, ear duct, thymus, small intestine, and pancreas. Single instances were also reported of tumors of the hematopoietic (blood-producing) system, heart, lung, mammary gland, pituitary gland, and peritoneum (NTP 2008). Male Wistar rats receiving daily subcutaneous injections of aristolochic acids developed urothelial carcinoma of the renal pelvis and malignant fibrohistiocytic sarcoma at the injection site (Debelle *et al.* 2002). A single intraperitoneal injection of aristolochic acids initiated liver carcinogenesis in male F344 rats that had also received treatment to stimulate proliferation of liver

cells (Rossiello *et al.* 1993). Aristolochic acids administered to female New Zealand White rabbits by intraperitoneal injection caused kidney tumors, a urinary-tract tumor, and mesothelioma of the peritoneal cavity (Cosyns *et al.* 2001).

Three studies investigated the carcinogenicity of extracts of *Aristolochia* (one study each for *A. manshuriensis*, *A. clematitidis*, and *A. contorta*) when administered to rats orally or by injection. Following oral administration, tumors of the forestomach and kidney were the most prevalent findings (Hwang *et al.* 2006), but one study reported tumors of the mammary gland, thyroid gland, and skin (Qiu *et al.* 2000), and one study reported injection-site polymorphocellular sarcoma (Ivic 1970). In one study, rats of both sexes were exposed to a weight-loss regimen of herbal ingredients that contained aristolochic acids; the males developed forestomach tumors (papilloma and squamous-cell carcinoma) (Cosyns *et al.* 1998).

Properties

Aristolochic acids are a family of nitrophenanthrene carboxylic acids that occur naturally in plants in the family Aristolochiaceae. The aristolochic acid content of plants or botanical preparations varies depending on the plant species, where it was grown, the time of year, and other factors. However, aristolochic acid I (also called aristolochic acid A) and its demethoxylated derivative, aristolochic acid II (also called aristolochic acid B) are the predominant forms. AA I is a crystalline solid that is slightly soluble in water. The molar extinction coefficient (ϵ) for AA I in ethanol is 6,500 at 390 nm, 12,000 at 318 nm, and 27,000 at 250 nm (O'Neil *et al.* 2006). Other selected physical and chemical properties of AA I are listed in the table below. No information was located on the physical or chemical properties of AA II other than its molecular weight of 311.3 (IARC 2002).

Property	Information for AA I
Molecular weight	341.3
Melting point	281°C to 286°C
Log K_{ow}	3.48

Source: IARC 2002.

Use

Aristolochia plants have been used since ancient times in traditional herbal medicines in many parts of the world, and aristolochic acids have been reported to have antibacterial, antiviral, antifungal, and antitumor effects (Kupchan and Doskotch 1962, Zhang *et al.* 2004). The name *Aristolochia* (meaning the best delivery or birth) is thought to be of ancient Greek origin and reflects centuries of use in obstetrics. Other traditional uses include treatment for snakebite, scorpion stings, fever, infection, diarrhea, and inflammation (Arlt *et al.* 2002, Jiménez-Ferrer *et al.* 2005). In contemporary medicine, *Aristolochia* plant extracts have been used in therapies for arthritis, gout, rheumatism, and festering wounds, but these uses were discontinued in Germany and other countries after the carcinogenic and mutagenic properties of aristolochic acids were first reported in the early 1980s (Arlt *et al.* 2002). Other uses of *Aristolochia* plants include cultivation as ornamental plants. Aristolochic acids also have been used in studies of toxicity and carcinogenicity and in biochemical studies as relatively selective inhibitors of the enzyme phospholipase A2 (NTP 2008).

Occurrence and Production

Aristolochic acids have been detected only in plant species belonging to the family Aristolochiaceae, primarily of the genera *Aristolochia* and *Asarum*. More than 30 *Aristolochia* species are native to the United States, and they are present in most states (USDA 2005). The

most widely distributed native species include *A. serpentaria* (Virginia snakeroot), *A. tomentosa* (woolly Dutchman's pipe), *A. macrophylla* (pipevine), and *A. clematitidis* (birthwort). In addition, some non-native species are grown as ornamentals or have escaped cultivation and become naturalized. Worldwide, there are an estimated 200 to 350 *Aristolochia* species, and virtually all of them contain aristolochic acids (NTP 2008). *Asarum* species (wild gingers) also are widely distributed in the United States. Plants of the genus *Hexastylis*, a group of rare plants endemic to the southeastern United States, were reported to have "unexpectedly high levels" of aristolochic acids (Schaneberg *et al.* 2002).

A number of studies have reported concentrations of AAs I and II in medicinal plants, including several species used in traditional Chinese medicine. Concentrations ranged from 3 to 12,980 ppm for AA I and from not detected to 6,325 ppm for AA II. In *Asarum* species, concentrations of AAs I and II ranged from trace levels to 3,377 ppm. Other studies detected AA IVa at concentrations of 79 to 3,360 ppm of crude drug, aristolactam I at 6 to 358 ppm, and aristolactam II at 14 to 91 ppm (NTP 2008). Hong *et al.* (1994) identified 11 aristolochic acid derivatives, including aristolactams and other compounds, in extracts from *Aristolochia cinnabarina* roots, and Wu *et al.* (1994) identified 14 aristolochic acid derivatives in extracts from stems and roots of *Aristolochia kankauensis*.

Aristolochic acids are produced commercially as reference standards and as research chemicals (IARC 2002). No data were found on U.S. producers or production volume, but in 2004, aristolochic acids were available from nine U.S. suppliers of aristolochic acid A (AA I), one supplier each of aristolochic acids B and D (AAs II and IV), three suppliers of aristolochic acid C (AA IIIa), and three suppliers of aristolochic acid, sodium salt (ChemSources 2004). No specific data on U.S. production, imports, or sales of botanical products that might contain aristolochic acids were found; however, many U.S. suppliers offer products that could contain aristolochic acids. Gold and Slone (2003) identified 112 botanical products that could contain aristolochic acids and were available for purchase over the Internet.

Exposure

Exposure to aristolochic acids may occur through ingestion as a result of intentional or inadvertent use of herbal or botanical products that contain *Aristolochia* or *Asarum* species. Exposure to aristolochic acids through ingestion of flour from wheat contaminated with *A. clematitidis* has been proposed as a cause for BEN. Herbal preparations are available in several forms (e.g., capsules, extracts, teas, or dried herbs). Exposure also could potentially occur through direct contact with the plants, either in their natural habitats or as cultivated ornamentals. Direct contact with the leaves of *Asarum canadense* (Canadian snakeroot or wild ginger) has been reported to cause dermatitis (PFAF 2005).

Schaneberg and Khan (2004) purchased from Internet Web sites 25 herbal products suspected of containing aristolochic acids, of which nine were manufactured in the United States and the rest in China. AAs I and II were detected in six of the products, each of which contained six or more types of plants. The U.S. Food and Drug Administration has reported recalls of products containing aristolochic acids beginning in 2000 and continuing with the report of a recall of two products in 2008 (Tou Tong San [Headache Formula] and Du Huo Ji Sheng Tang [Du Huo Joint Relief]) (FDA 2008). Two herbal remedies prepared from *Aristolochia debilis* or *A. contorta* appeared in the official 2005 Chinese pharmacopeia, and three additional entries for drugs derived from *A. debilis*, *A. fangchi*, and *A. manshuriensis* were cancelled in 2003 and 2004 because the content of aristolochic acid in the drugs was high enough to cause AAN (Zhang *et al.* 2006).

In addition to the intentional uses of aristolochic acid-containing plants, herbal preparations can pose a number of quality-related problems, which can lead to inadvertent exposures. These include contamination with prohibited or restricted substances, substitution of ingredients, contamination with toxic substances, and differences between the labeled and actual product contents (MCA 2002).

The complexity of herbal nomenclature systems used in traditional medicines (particularly traditional Chinese medicines) can lead to confusion and increased risk of inadvertent exposure to aristolochic acids (Flurer *et al.* 2001), which was reported for cases in Hong Kong (Liang *et al.* 2006), Belgium (Vanherweghem 1998), and Singapore (Koh *et al.* 2006). Substitutions arising because of name confusion have also been reported between botanicals used in Japanese herbal medicines and botanicals with similar names used in Chinese herbal medicines (Tanaka *et al.* 2001, EMEA 2005). The most extensive exposure resulting from name confusion occurred in the early 1990s in Belgium, where *A. fangchi* was inadvertently substituted for *Stephania tetrandra* to prepare diet pills. The Chinese name for *S. tetrandra* is “fang ji,” which is similar to the name for aristolochic acid-containing *A. fangchi* (“guang fang ji”). An estimated 1,500 to 2,000 individuals (primarily women) were exposed to the *Stephania*-labeled powders that contained aristolochic acids ranging from below the detection limit (< 0.02 mg/g) to 2.9 mg/g (2,900 ppm) (Vanherweghem 1998). The resulting maximum dose of aristolochic acids was estimated at 0.025 mg/kg received over an average of 13 months (Grollman *et al.* 2009).

For botanical products, high concentrations or intake of aristolochic acids have been reported in studies from China (AA I at 700 ppm, with estimated AA intake of 110 mg), Taiwan (AA I at up to 19.97 nmol/g and AA II at up to 3.95 nmol/g), Hong Kong (intake of herb from 100 mg to 800 g), Japan (total AA at up to 15.1 ppm), Australia (AA I at up to 40 ppm and AA II at up to 210 ppm), and Switzerland (AA I at up to 440 ppm) (NTP 2008). Chinese patients who developed chronic renal failure had ingested an estimated 0.7 to 1.5 mg of aristolochic acids per day intermittently for 1 to 10 years (Grollman *et al.* 2009).

No estimates were found of the number of people in the United States who are exposed to aristolochic acids in herbal medicines, but two U.S. cases of renal failure resulting from ingestion of herbal products containing aristolochic acids have been reported (Meyer *et al.* 2000, Consumer Reports 2004, Grollman *et al.* 2007). The use of all complementary and alternative medicines increased in the 1990s and 2000s (Barnes *et al.* 2004, Bent and Ko 2004). The Centers for Disease Control and Prevention reported that 10% of adults in the United States ingested herbal medicines in 1999 (Straus 2002), and the total spent on herbs and other botanical remedies in 2001 was \$4.2 billion (Marcus and Grollman 2002).

The possibility also exists for exposure to aristolochic acids in food. It has been suggested that contamination of wheat flour by *Aristolochia* species growing as weeds adjacent to wheat fields might be responsible for BEN (Ivic 1970, Hranjec *et al.* 2005). Indeed, seeds of *A. clematitis* have been found commingled with wheat grain during harvest in regions where BEN is endemic (Grollman and Jelaković 2007). It has been estimated that at least 25,000 individuals are suspected of having BEN and that over 100,000 individuals residing in endemic regions could be at risk (DeBelle *et al.* 2008). As noted above, AA-DNA adducts were found in kidney tissue from BEN patients and in urothelial and kidney (renal cortical) tissues from BEN patients who had upper-urinary-tract urothelial cancer. Because *Aristolochia* species are widely distributed and wheat can be traded internationally, there is the potential for worldwide exposure from this source; however, no data were found to support this hypothesis.

Extracts from *Asarum canadense* and *Aristolochia serpentaria* are permitted for use in the United States as flavoring substances in foods or beverages (FDA 2003); *A. serpentaria* has been reported to be used as a spice and to flavor liqueurs or bitters, such as Angostura or Boonekamp bitters, but no information was found on the concentrations of aristolochic acid in these products.

Although occupational exposure to aristolochic acids has not been documented, herbalists potentially are exposed while gathering plants or while preparing or applying botanical products. Gardeners, landscapers, or nursery workers who handle or transplant *Aristolochia* or *Asarum* plants could potentially be exposed to aristolochic acids. Handling *Aristolochia* or *Asarum* plants could result in dermal exposure, which, as of 2010, has been associated only with dermatitis. To reduce the likelihood of accidental ingestion, workers should wash their hands before eating, drinking, or smoking.

Regulations

Food and Drug Administration (FDA)

Federal Food, Drug, and Cosmetic Act as amended by the Dietary Supplement Health and Education Act

Manufacturers and distributors as of 2007 must record adverse events and report to the FDA serious adverse events reported to them about their products.

Label requirements for dietary supplements have been established.

Manufacturers must establish and meet specifications for identity, purity, strength, and composition and for limits on contamination of dietary supplements under current Good Manufacturing Practices (cGMP) regulations published in 2007.

Warnings and Alerts

Food and Drug Administration (FDA)

Warnings issued in 2000 and 2001 (FDA 2000, 2001a,b) covered botanical products that contain aristolochic acids:

- Practitioners who prescribe botanical remedies urged to discard those products containing aristolochic acids.
- Manufacturers and distributors urged to ensure that botanical products are free of aristolochic acids.
- Consumers urged to immediately discontinue use of botanical products that contain or likely contain aristolochic acids.

An import alert issued in 2000 and revised in 2007 provided for the detention of products labeled as *Aristolochia* or any that could be confused with it unless analytical evidence shows no aristolochic acids.

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Arsenic and Inorganic Arsenic Compounds

CAS No. 7440-38-2 (Arsenic)

No separate CAS No. assigned for inorganic arsenic compounds

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as As

Carcinogenicity

Arsenic and inorganic arsenic compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans.

Cancer Studies in Humans

Epidemiological studies and case reports of humans exposed to arsenic or arsenic compounds for medical treatment, in drinking water, or occupationally have demonstrated that exposure to arsenic and inorganic arsenic compounds increases the risk of cancer. Cancer tissue sites include the skin, lung, digestive tract, liver, urinary bladder, kidney, and lymphatic and hematopoietic systems. Skin cancer has been reported in individuals exposed to arsenic for therapeutic reasons, sometimes in combination with cancer at other tissue sites, such as blood-vessel cancer (angiosarcoma) of the liver, intestinal and urinary-bladder cancer, and meningioma (tumors of the membranes covering the central nervous system). However, only skin cancer has been clearly associated with medical use of arsenic in epidemiological studies (IARC 1973, 1980).

Several studies have reported an association between skin cancer and exposure to arsenic in drinking water. Epidemiological studies conducted in Taiwan, in an area where blackfoot disease (a disorder of the peripheral blood vessels caused by arsenic) is endemic, found that exposure to drinking water containing arsenic at concentrations ranging from 0.35 to 1.14 mg/L increased the risks of urinary-bladder, kidney, skin, lung, liver, and colon cancer. Occupational exposure to inorganic arsenic compounds, especially in mining and copper smelting, consistently has been associated with increased risk of lung cancer (predominantly adenocarcinoma, with a slight excess of small-cell cancer); the risk of lung cancer increased with increasing cumulative exposure to arsenic. Exposure of smelter workers to arsenic also has been associated with increased risks of cancer of the kidney, digestive tract, and lymphatic and hematopoietic systems. Epidemiological studies and case reports of workers in other industries exposed to arsenic, such as glass workers, hat makers, and pesticide workers, also have reported excesses of cancer (mainly lung and skin cancer) (IARC 1973, 1980).

Since arsenic was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, numerous epidemiological studies have evaluated the carcinogenicity of arsenic in drinking water. Several studies have reported exposure-response relationships for several types of cancer, including urinary-bladder, kidney, lung, and skin cancer (Cantor 1997, Ferreccio *et al.* 2000). A few studies have suggested that exposure to arsenic in drinking water is associated with cancer at additional tissue sites, including prostate cancer in men and nasal cancer in both sexes (Cantor 1997). Some evidence suggests that arsenic exposure is more strongly associated with transitional-cell carcinoma of the urinary bladder than with other types of urinary-bladder cancer (Guo *et al.* 1997, Chiou *et al.* 2001). Most studies found associations with cancer of the lung, urinary bladder, or prostate at lower arsenic concentrations than those reported in the Taiwanese study cited above; however, the evidence for carcinogenic effects at very low concen-

trations of arsenic is inconclusive (Kurttio *et al.* 1999, Lewis *et al.* 1999, Ferreccio *et al.* 2000, Chiou *et al.* 2001, Steinmaus *et al.* 2003, Bates *et al.* 2004). In some studies of urinary-bladder cancer, an association with arsenic exposure was observed only when the analysis was limited to smokers and to arsenic exposures that had occurred at least 40 years previously (Steinmaus *et al.* 2003, Bates *et al.* 2004).

Cancer Studies in Experimental Animals

Metallic arsenic, arsenic trioxide, sodium arsenite, sodium arsenate, potassium arsenite, lead arsenate, calcium arsenate, and pesticide mixtures containing arsenic have been tested for carcinogenicity in experimental animals (IARC 1980, 1987). Mice and rats were exposed to various arsenic compounds by oral administration and subcutaneous injection. Mice were also exposed by dermal application, inhalation, and intravenous injection, and rats by intratracheal instillation and femoral intramedullary injection. In other studies, dogs were exposed orally, hamsters by intratracheal instillation, and rabbits by intramedullary injection. In rats, oral exposure to arsenic trioxide caused stomach cancer (adenocarcinoma), and intratracheal instillation of a pesticide mixture containing calcium arsenate compounds caused a high incidence of lung cancer (adenocarcinoma). Benign and malignant lung tumors (adenoma and carcinoma) were also observed at low incidences in hamsters following intratracheal instillation of arsenic trioxide, and benign lung tumors (adenoma) occurred in neonatal mice subcutaneously injected with arsenic trioxide following prenatal exposure via a single subcutaneous injection during gestation. Lymphocytic leukemia and lymphoma were observed in mice given weekly intravenous injections of an aqueous solution of sodium arsenate for 20 weeks and in female mice and their offspring following subcutaneous injections of sodium arsenate throughout pregnancy. In most of the other studies in experimental animals, no tumors were observed, or the results were inconclusive.

Properties

Arsenic is a naturally occurring semimetallic element with an atomic weight of 74.9. Pure arsenic (which rarely is found in nature) exists in three allotropic forms: yellow (alpha), black (beta), and gray (gamma) (HSDB 2009). Many inorganic arsenic compounds are found in the environment, frequently occurring as the sulfide form in complex minerals containing copper, lead, iron, nickel, cobalt, and other metals. Arsenic compounds occur in trivalent and pentavalent forms; common trivalent forms are arsenic trioxide and sodium arsenite, and common pentavalent forms are arsenic pentoxide and the various arsenates. Arsenic and arsenic compounds occur in crystalline, powder, amorphous, or vitreous forms. Elemental arsenic has a specific gravity of 5.73, sublimes at 613°C, and has a very low vapor pressure of 1 mm Hg at 373°C. Many of the inorganic arsenic compounds occur as white, odorless solids with specific gravities ranging from about 1.9 to over 5. Arsenic trioxide, the most common arsenic compound in commerce, melts at 312°C and boils at 465°C (ATSDR 2007). In water, elemental arsenic is insoluble, calcium arsenate and arsenites are sparingly soluble, and arsenic trioxide, arsenic pentoxide, and other arsenicals are soluble. Arsenic pentoxide, potassium arsenite, and the sodium salts are soluble in ethanol. Arsenic, arsenic pentoxide, arsenic trioxide, the calcium arsenites, lead arsenate, and potassium arsenate are soluble in various acids. When heated to decomposition, arsenic compounds emit toxic arsenic fumes (HSDB 2009).

Use

Inorganic arsenic compounds were widely used as pesticides from the mid 1800s to the mid 1900s and were used in medicine until the 1970s, primarily for treatment of leukemia, psoriasis, and asthma. The use

of arsenic for treatment of acute promyelocytic leukemia resumed in the 1990s. By the mid 1970s, arsenic use was shifting from pesticides to wood preservatives, and by 1980, wood preservatives were the primary use. Total agricultural-chemical use (in pesticides and fertilizers) declined to about 15% to 20% of total arsenic consumption by the early 1990s and has remained at about 4% since 1995 (Edelstein 1994, Reese 1998, ATSDR 2007, Brooks 2009).

Since the mid 1990s, arsenic trioxide used in wood preservation has accounted for 86% to 90% of total U.S. arsenic consumption. Wood treated with chromated copper arsenate (CCA), known as "pressure-treated wood," has been used widely to protect utility poles, building lumber, and foundations from decay and insect attack. However, a voluntary phase-out of CCA for certain residential uses (e.g., in wood for decks, play structures, fencing, and boardwalks) that went into effect December 31, 2003, has reduced this use of arsenic. CCA continues to be used in wood products for industrial use. Other uses of arsenic in the 1990s included use in glass (3% to 4%) and non-ferrous alloys (1% to 4%) (ATSDR 2007, Brooks 2009).

By the 1990s, there was renewed interest in the use of arsenic for treatment of acute promyelocytic leukemia (ATSDR 2007). Arsenic trioxide is approved by the U.S. Food and Drug Administration for treating this type of leukemia when other chemotherapy treatments have failed (MedlinePlus 2009). Arsenic is also used in the production of lead alloys used in lead-acid batteries. It may be added to alloys used for bearings, type metals, lead ammunition, and automotive body solder, and it may be added to brass to improve corrosion resistance. High-purity arsenic is used in a variety of semiconductor applications, including solar cells, light-emitting diodes, lasers, and integrated circuits (ATSDR 2007).

Production

Before 1985, U.S. arsenic production varied widely, peaking at 24,800 metric tons (54.7 million pounds) in 1944. Although the United States is the world's leading consumer of arsenic, arsenic has not been produced domestically since 1985, when production of 2,200 metric tons (4.9 million pounds) was reported (Brooks 2009, USGS 2009). U.S. apparent consumption of arsenic was estimated at 7,340 metric tons (16.2 million pounds) in 2006, declining steadily to 3,600 metric tons (7.9 million pounds) in 2009 (USGS 2010). All arsenic metal and compounds consumed in the United States now are imported. U.S. imports of arsenic and arsenic compounds averaged about 8,300 metric tons (18.3 million pounds) from 1935 to 1959, 11,200 metric tons (24.7 million pounds) from 1960 to 1985, and 19,000 metric tons (42 million pounds) from 1986 to 2009 (USGS 2009, 2010). Since 2004, imports have ranged from a high of 10,500 metric tons (23.1 million pounds) in 2006 to a low of 5,190 metric tons (11.4 million pounds) in 2008, and were 6,575 metric tons (14.5 million pounds) in 2009, with arsenic trioxide accounting for 94% and arsenic metal accounting for 6% of imports (USGS 2010). U.S. exports peaked at 4,230 metric tons (9.3 million pounds) in 1941 and reached a low of 36 metric tons (79,000 lb) in 1996. Exports have increased dramatically since 2004. Exports classified as arsenic metal may include arsenic-containing e-waste, such as computers and other electronics destined for reclamation and recycling in other countries. Since U.S. arsenic production ended in 1985, exports have been highest in 2005, at 3,270 metric tons (7.2 million pounds). In 2009, exports totaled 2,980 metric tons (6.6 million pounds) (Brooks 2009, USGS 2009, 2010).

Exposure

The general population is exposed to arsenic and arsenic compounds primarily through consumption of foods. The estimated daily dietary intake of inorganic arsenic ranges from about 1 to 20 µg; however, the

average daily dietary intake of arsenic in all forms is about 40 µg. The highest levels of arsenic (in all forms) are detected in seafood, rice, rice cereal, mushrooms, and poultry. Inorganic arsenic was reported in the tissue of livestock that had been administered arsenic drugs or feed additives (ATSDR 2007), and U.S. Department of Agriculture researchers reported that consumption of meat from chickens fed an organic arsenic compound (4-hydroxy-3-nitrophenylarsonic acid) could result in ingestion of 21.1 to 30.6 µg of inorganic arsenic per day for people in the 99th percentile of consumption level (Lasky *et al.* 2004). This organic arsenic compound, which is used as an antimicrobial in animal and poultry feeds, is found mostly unchanged in poultry litter; however, under anaerobic conditions, *Clostridium* bacteria can transform it to release arsenate (Stolz *et al.* 2007). The release of inorganic arsenic from large quantities of poultry litter could have a detrimental effect on soil and water quality (Jackson *et al.* 2003). Arsenic used as pigments in paints can be ingested through contamination of hands, fingernails, food, cups, or cigarettes or through the practice of holding paint brushes in the mouth (HSDB 2009).

Potential exposure to arsenic also occurs through the consumption of drinking water contaminated with arsenical pesticides, natural mineral deposits, or arsenical chemicals that were disposed of improperly (ATSDR 2007). Natural soil concentrations of arsenic (in all forms) typically range from 0.1 to 40 mg/kg, averaging 5 to 6 mg/kg. Through natural processes, arsenic in soil can be released to groundwater or surface water. In the United States, mean arsenic concentrations generally are higher in groundwater systems (wells) than in surface-water systems. Arsenic concentrations in groundwater and surface water are lowest in the mid-Atlantic and southeastern regions, intermediate in New England, the Midwest, and the south-central and north-central regions, and highest in the West (EPA 2000). U.S. drinking water contains arsenic at an average concentration of 2 µg/L; however, 12% of groundwater systems in the West and 12% of surface-water systems in the north-central region contain arsenic at levels exceeding 20 µg/L (ATSDR 2007). In addition, several states have groundwater systems with maximum levels of arsenic exceeding 50 µg/L, including California (99 µg/L), Nevada (150 µg/L), and Texas (86 µg/L) (EPA 2000). Reported arsenic concentrations in groundwater in Fairbanks, Alaska, ranged up to 1,670 µg/L (USGS 2001).

The general population may also be exposed to arsenic compounds emitted to the air by pesticide manufacturing facilities, smelters, cotton gins, glass manufacturing operations, cigarette smoking, burning of fossil fuels, and other sources (ATSDR 2007). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of arsenic between 1988 and 2007 ranged from 77,000 lb to over 77 million pounds, while releases of arsenic compounds ranged from 3.4 million to 568 million pounds. Releases showed no clear trends over this period. In 2007, 51 facilities released arsenic, and 245 facilities released arsenic compounds (TRI 2009).

Inhalation and dermal contact are the primary routes of occupational exposure to arsenic. Because arsenic is no longer produced in the United States and many uses of arsenical pesticides have been banned, the number of workers exposed to arsenic likely has decreased since the early 1980s. Nevertheless, occupational exposure to arsenic (including forms other than inorganic compounds) is likely in several industries, including nonferrous smelting, wood preservation, glass manufacturing, electronics, and production and use of agricultural chemicals (ATSDR 2007). No recent occupational exposure surveys were found; however, the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 57,000 workers, including over 11,000 women, potentially were exposed to arsenic, arsenic pentoxide, arsenic trioxide, arsenic acid, arsenic oxide, arsenic sulfide, or arsenic trichloride (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Fireworks devices shall not contain arsenic sulfide, arsenates, or arsenites.

Department of Transportation (DOT)

Inorganic arsenic compounds are considered hazardous materials, and orthoarsenic acid is considered a marine pollutant; special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Arsenic compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Arsenic compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb for arsenous trichloride; = 1,000 lb for arsine.

Urban Air Toxics Strategy: Arsenic compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Limits have been established for arsenic in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Liquid hazardous wastes containing arsenic and/or compounds at levels \geq 500 mg/L (as As) are prohibited from underground injection.

Effluent Guidelines: Arsenic and arsenic compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.018 μ g/L for arsenic; based on fish or shellfish consumption only = 0.14 μ g/L for arsenic.

Numerous inorganic arsenic compounds are designated hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for arsenic, arsenic acid, arsenic disulfide, arsenic pentoxide, arsenic trioxide, arsenic trisulfide, arsenic oxide, arsenic trichloride, sodium arsenate, lead arsenate, calcium arsenate, potassium arsenate, sodium arsenite, potassium arsenite, calcium arsenite.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Arsenic and arsenic compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for arsenic pentoxide, arsenic disulfide, arsenic trisulfide, arsenic trioxide, arsenous oxide, sodium arsenate, calcium arsenate, arsenous trichloride, sodium arsenite, potassium arsenite, arsenic; = 100 lb for arsine.

Threshold planning quantity (TPQ) = 100 lb for arsine; = 500 lb for arsenous trichloride; = 100 lb/10,000 lb for arsenic pentoxide, arsenic trioxide, arsenous oxide (solids in powder form with particle size < 100 μ m or in solution or molten form/all other forms); = 500 lb/10,000 lb for calcium arsenate, sodium arsenite, potassium arsenite; = 1,000 lb/10,000 lb for sodium arsenate.

Federal Insecticide, Fungicide, and Rodenticide Act

The tolerance for residues of arsanilic acid (a plant regulator) on grapefruit = 2 ppm (0.7 ppm total arsenic).

The label of each pesticide must state whether it contains arsenic in any form and the percentage of total and water-soluble arsenic.

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate (CCA).

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of arsenic or its compounds = P010, P011, P012, F032, F034, F035, K031, K060, K084, K101, K102, K161, K171, K172, K176.

Arsenic and arsenic compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.01 mg/L for arsenic.

Food and Drug Administration (FDA)

Maximum permissible level of arsenic in bottled water = 0.01 mg/L.

Specified color additives may be used in food, drugs, and cosmetics subject to limitations on arsenic levels as prescribed in 21 CFR 73 and 74.

Maximum arsenic levels in various specified food additives range from 0.1 to 3 ppm.

All drug products containing potassium arsenite are withdrawn from the market.

Labels must be put on drugs containing arsenic stating that prolonged use could cause serious injury and to keep out of the reach of children.

Tolerances for residues of arsenic in swine, poultry meat and by-products, and chicken eggs range from 0.5 to 2 ppm.

Maximum levels allowed in food additives permitted in feed and drinking water for animals range from 3 to 75 ppm.

Arsenic trioxide is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.010 mg/m³.

Comprehensive standards for occupational exposure to arsenic have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 mg/m³ for inorganic arsenic compounds; = 0.005 ppm for arsine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 5 mg/m³ for inorganic compounds (as As).

Ceiling recommended exposure limit = 0.002 mg/m³ (15 min) for inorganic compounds (as As).

Inorganic arsenic compounds are listed as potential occupational carcinogens.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Asbestos

CAS No. 1332-21-4

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Asbestos and all commercial forms of asbestos are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies in humans have shown that exposure to asbestos causes respiratory-tract cancer, mesothelioma of the lung and abdominal cavity (pleural and peritoneal mesothelioma), and cancer at other tissue sites. Case reports and epidemiological studies have found that occupational exposure to chrysotile, amosite, anthophyllite, mixtures containing crocidolite, and various complex mixtures of asbestos increases the risk of lung cancer (the various forms of asbestos are identified and described below, under Properties). The risk of lung cancer was increased up to sixfold in vermiculite miners exposed to tremolite and actinolite. Mesothelioma and digestive-tract cancer were observed in workers occupationally exposed to crocidolite, amosite, and chrysotile; however, the results for digestive-tract cancer were inconsistent among studies. An excess of laryngeal cancer was reported in studies of shipyard workers, chrysotile miners, insulation workers, and other workers exposed to asbestos. People living near asbestos factories or mines or living with asbestos workers also developed mesothelioma. However, no clear association was found between cancer risk and exposure to asbestos in drinking water. Co-exposure to asbestos and tobacco smoking increased the risk of lung cancer in a synergistic manner (i.e., the effects of co-exposure on risk were multiplicative, rather than additive). The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of asbestos in humans (IARC 1977, 1987).

Since asbestos was listed in the *First Annual Report on Carcinogens*, the evidence for the carcinogenicity of asbestos has been reevaluated by the Institute of Medicine (IOM) of the National Academy of Sciences in 2006 (NAS 2006) and by IARC in 2009 (Straif *et al.* 2009). IARC concluded that exposure to all forms of asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite) was associated with an increased risk of lung cancer and mesothelioma. In addition, it concluded that there was sufficient evidence from epidemiological studies that asbestos also caused cancer of the larynx and ovary, as well as limited evidence that it caused cancer of the colorectum, pharynx, and stomach. In general, these conclusions were consistent with the IOM evaluation, which found sufficient evidence that exposure to asbestos caused cancer of the larynx and suggestive evidence that it caused cancer of the pharynx, stom-

ach, and colorectum (NAS 2006). The IOM did not review studies on lung cancer and mesothelioma.

Cancer Studies in Experimental Animals

All commercial forms of asbestos have been shown to cause cancer in several species of experimental animals by various routes of exposure (IARC 1977, 1987). Inhalation exposure to chrysotile, crocidolite, amosite, anthophyllite, or tremolite caused mesothelioma and lung cancer (carcinoma) in rats. Intraperitoneal injection of various types of asbestos caused mesothelioma in rats and hamsters, and intraperitoneal injection of chrysotile, crocidolite, or amosite caused peritoneal tumors, including mesothelioma, in mice and rats. The incidence of abdominal tumors was increased by intraperitoneal injection of crocidolite in hamsters and actinolite or tremolite in rats. When filter material containing chrysotile was added to the diet of rats, the overall incidence of malignant tumors (including kidney, lung, and liver tumors) was increased. Oral administration of amosite, tremolite, or crocidolite did not cause tumors in rats, nor did oral administration of amosite or chrysotile in hamsters (NTP 1985, IARC 1987). Dietary administration of chrysotile asbestos fibers of short or intermediate lengths did not cause tumors in female rats, but dietary exposure to the intermediate-length fibers resulted in a low incidence of benign adenomatous polyps of the large intestine in male rats (NTP 1985).

Asbestos and the polycyclic aromatic hydrocarbon benzo[*a*]pyrene administered alone by intratracheal injection did not cause tumors in rats, but when co-administered caused lung tumors and mesothelioma (IARC 1977). Synergistic effects on tumor induction also were observed following co-administration of asbestos and benzo[*a*]pyrene or asbestos and *N*-nitrosodiethylamine to hamsters (IARC 1987).

IARC (1977, 1987) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of asbestos, including the following forms: actinolite, amosite, anthophyllite, chrysotile, crocidolite, and tremolite. Since asbestos was reviewed for listing in the *First Annual Report on Carcinogens* and by IARC, intrabronchial instillation of chrysotile has been shown to cause pulmonary and pleural mesothelioma in rats (Fasske 1988).

Properties

Asbestos is the generic name for a group of six naturally occurring fibrous silicate minerals, including the fibrous serpentine mineral chrysotile and the five fibrous amphibole minerals actinolite, amosite, anthophyllite, crocidolite, and tremolite. Asbestos minerals possess a number of properties useful in commercial applications, including heat stability, thermal and electrical insulation, wear and friction characteristics, tensile strength, the ability to be woven, and resistance to chemical and biological degradation. The forms are ranked from greatest to least tensile strength as follows: crocidolite, chrysotile, amosite, anthophyllite, tremolite, and actinolite. Their ranking from greatest to least acid resistance is tremolite, anthophyllite, crocidolite, actinolite, amosite, and chrysotile. The forms that have been used commercially are chrysotile, anthophyllite, amosite, and crocidolite (IARC 1977, ATSDR 2001, HSDB 2009).

Chrysotile, the most abundant form of asbestos in industrial applications, occurs naturally in fiber bundle lengths ranging from several millimeters to over 10 cm (Virta 2002a). Chrysotile has an idealized chemical composition of $Mg_3Si_2O_5(OH)_4$ and occurs as a curled sheet silicate, which wraps around itself in a spiral, forming a hollow tubular fiber. The hydroxyl group may, rarely, be replaced by oxygen, fluorine, or chlorine. In addition, small amounts of iron, aluminum, nickel, calcium, chromium, manganese, sodium, or potassium may be present as impurities. Natural chrysotiles occur with a range of phys-

ical properties. Chrysotiles may be white, gray, green, or yellowish, with a silky luster. Although chrysotile fibers are more flexible than the amphiboles, fibers from different geological locations may differ in flexibility. Chrysotile fibers have a net positive surface charge and form a stable suspension in water. The fibers degrade in dilute acids (IARC 1973, 1977, IPCS 1986).

The amphibole forms of asbestos consist of chain structures, with nine structural sites that accommodate cations. Amphibole crystals consist of two chains based on Si_4O_{11} units, linked by a band of cations. The principal cations are magnesium, iron, calcium, and sodium, and their ratios determine the mineral species. The chemical composition and physical properties vary over a wide range, and the chemical composition of a field sample seldom matches the idealized formula. Amphibole fibers do not divide into fibrils as small in diameter or as symmetrical as chrysotile fibers, and they do not have a hollow central core. They have a negative surface charge in water (IPCS 1986, HSDB 2009).

Amosite is ash gray, greenish, or brown and is somewhat resistant to acids. It tends to occur with more iron than magnesium, at a ratio of approximately 5.5 to 1.5. The fibers are long, straight, coarse, and somewhat flexible (less so than chrysotile or crocidolite) (IARC 1973, 1977, IPCS 1986).

Anthophyllite is grayish white, brown-gray, or green and is very resistant to acids. It is relatively rare and occasionally occurs as a contaminant in talc deposits. The fibers are short and very brittle (IARC 1973, 1977, IPCS 1986).

Crocidolite is lavender or blue and has good resistance to acids, but less heat resistance than other asbestos fibers. Its fibers typically are shorter and thinner than those of other amphiboles, but not as thin as chrysotile fibers. The fibers have fair to good flexibility and fair spinnability. Crocidolite usually contains organic impurities, including low levels of polycyclic aromatic hydrocarbons (IARC 1973, 1977, IPCS 1986).

Tremolite is a calcium-magnesium amphibole, and actinolite is an iron-substituted derivative of tremolite. Both occur in asbestos and non-asbestos forms. Tremolite is a common contaminant in chrysotile and talc deposits, and actinolite is a common contaminant in amosite deposits. Tremolite is white to gray, and actinolite is pale to dark green. Both are brittle; tremolite is resistant to acids, but actinolite is not (IARC 1977, IPCS 1986).

Use

Although asbestos use dates back at least 2,000 years, modern industrial use began around 1880. Use of asbestos peaked in the late 1960s and early 1970s, when more than 3,000 industrial applications or products were listed. Asbestos has been used in roofing, thermal and electrical insulation, cement pipe and sheets, flooring, gaskets, friction materials, coatings, plastics, textiles, paper, and other products (ATSDR 2001, HSDB 2009). The U.S. Consumer Product Safety Commission banned use of asbestos in general-use garments, but asbestos may be used in fire-fighting garments if they are constructed to prevent release of asbestos fibers (HSDB 2009). Domestically used asbestos fibers are classified into seven quality categories or grades. Grades 1, 2, and 3 include the longer, maximum-strength fibers and generally are used in the production of textiles, electrical insulation, and pharmaceutical and beverage filters. Grades 4, 5, and 6 are medium-length fibers used in the production of asbestos-cement pipes and sheets, clutch facings, brake linings, asbestos paper, packaging, gaskets, and pipe coverings. Grade 7 includes short fibers generally used as reinforcers in plastics, floor tiles, coatings and compounds, some papers, and roofing felts (OSHA 1986).

The four commercially important forms of asbestos have been chrysotile, amosite, anthophyllite, and crocidolite (IARC 1973); however, commercial use of anthophyllite was discontinued by the 1980s (IPCS 1986, HSDB 2009). Chrysotile, amosite, and particularly crocidolite all have extremely high tensile strengths and are used extensively as reinforcers in cements, resins, and plastics. Although chrysotile is most adaptable to industrial use, crocidolite and amosite are particularly useful in combination with chrysotile for adding specific properties, such as rigidity (OSHA 1986). By the 1990s, chrysotile accounted for more than 99% of U.S. asbestos consumption (ATSDR 2001). By 2008, chrysotile was the only type of asbestos used in the United States (Virta 2008); 64% of chrysotile used was categorized as grade 7 asbestos (with fiber lengths less than 3 mm), followed by grades 4, 5, and 3 (Virta 2002a, 2009).

In 1973, when U.S. consumption of asbestos was at its peak, the major markets included asbestos cement pipe (24%), flooring (22%), roofing (9%), friction products, such as automobile brakes and clutches (8%), and packing and gaskets (3%) (Virta 2002a). In 2009, roofing products accounted for about 65% of U.S. consumption; the remaining 35% was attributed to "other uses" (USGS 2010).

Production

U.S. demand for asbestos increased dramatically from 1900 to the early 1970s. By 1950, the United States was the world's largest user of asbestos. However, asbestos demand declined rapidly after 1973 as health and liability issues became apparent (Virta 2002a). Before the 1980s, asbestos was produced in California, Arizona, North Carolina, and Vermont; however, most of these facilities suspended mining operations in the 1970s, and the last U.S. asbestos mine closed in 2002 (ATSDR 2001, Virta 2002b). U.S. production of asbestos decreased from a high of 136,000 metric tons (300 million pounds) in 1973 to 2,720 metric tons (6 million pounds) in 2002 (USGS 2009). U.S. asbestos consumption declined from a maximum of 803,000 metric tons (1.8 billion pounds) in 1973 to 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). In 2010, two U.S. suppliers of asbestos were identified (ChemSources 2009). Most of the asbestos used in the United States is imported from Canada (Virta 2008). U.S. imports of asbestos peaked in 1973, at 718,000 metric tons (1.6 billion pounds) and totaled 715 metric tons (1.6 million pounds) in 2009 (USGS 2009, 2010). U.S. asbestos exports peaked in 1981 at 64,400 metric tons (142 million pounds), declining to 55 metric tons (121,000 pounds) in 2009.

Exposure

The primary routes of potential human exposure to asbestos are inhalation and ingestion. Dermal absorption of asbestos is minimal, but dermal contact may lead to secondary ingestion or inhalation of dust. Asbestos fibers vary with respect to size (length and diameter) and chemical composition. These differences are known to affect deposition, movement, and clearance from the body and carcinogenic potency. Fiber diameter is the most important factor affecting penetration and deposition in the lungs. Thin fibers have the greatest inhalation potential and deposit deep within the lungs. Fiber length, surface chemistry, and other properties affect biological activity. Fibers longer than 8 μm with a diameter of less than 1.5 μm are the most potent carcinogens (IPCS 1986).

Asbestos is released to the environment from both natural and anthropogenic sources and has been detected in indoor and outdoor air, soil, drinking water, food, and medicines. Because asbestos products were used so widely, the entire U.S. population potentially is exposed to some degree; however, the potential for exposure continues to decline, because asbestos mining has stopped, and asbestos products are

being eliminated from the market. Releases from asbestos materials in buildings and vehicle brake linings account for substantial emissions of asbestos into the air. Demolition of buildings with asbestos insulation or fireproofing may cause high atmospheric concentrations for relatively short periods. Environmental asbestos concentrations vary widely; therefore, it is not possible to accurately calculate human exposure levels except on a site-by-site basis. People may be exposed to higher-than-average levels of asbestos in air if they live near asbestos-containing waste sites or asbestos-related industries, if they use asbestos-containing products, or if they live or work in buildings with deteriorating asbestos insulation or that have undergone poorly performed asbestos removal (ATSDR 2001). In the past, families of asbestos workers potentially were exposed to high fiber levels from contaminated clothing brought home for laundering. People living in households with asbestos workers were found to have significantly elevated lung burdens of asbestos, often in the same range as found in individuals occupationally exposed to asbestos, such as shipyard workers. The asbestos-fiber burdens of occupants of a building containing asbestos insulation, on the other hand, were comparable to those of individuals with no known occupational exposure to asbestos (IARC 1977, Roggli and Longo 1991).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of asbestos are to landfills. Reported releases declined about 80% from 1988 to 1997, then increased between 1998 and 2001, when 18.2 to 24.4 million pounds was released to landfills annually. Releases returned to lower levels after 2002. In 2007, 30 industrial facilities (mostly waste-management companies) reported releasing or disposing of about 10.5 million pounds of friable (readily crumbled) asbestos (TRI 2009).

In the past, occupational exposure occurred primarily during the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. Occupational exposure still occurs among workers who use asbestos end products, such as asbestos insulation workers, brake repair and maintenance workers, building demolition workers, and asbestos abatement workers (IARC 1977, ATSDR 2001, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 215,265 workers, including 9,727 women, potentially were exposed to asbestos and that 92,033 workers, including 13,262 women, potentially were exposed to chrysotile (NIOSH 1990). In 1990, the U.S. Occupational Safety and Health Administration estimated that about 568,000 workers in production and services industries and 114,000 workers in construction industries potentially were exposed to asbestos (ATSDR 2001). No more recent occupational exposure estimates were found.

Regulations

Consumer Product Safety Commission (CPSC)

Consumer patching compounds containing intentionally added respirable, free-form asbestos are banned.

Artificial emberizing materials (ash and embers) containing respirable free-form asbestos are banned.

General-use garments containing asbestos (other than those needed for personal protection and constructed so that asbestos fibers will not become airborne) are banned.

Certain household products containing intentionally added asbestos that release asbestos fibers are subject to cautionary labeling requirements.

Department of Transportation (DOT)

Asbestos is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 7 million fibers per liter.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 7 million fibers per liter for fibers longer than 10 μm .

Toxic Substances Control Act

Rules have been established for identifying, analyzing, and disposing of asbestos found in schools, and prohibitions on the manufacturing and import of asbestos products have been established.

Mine Safety and Health Administration

Permissible exposure limit (PEL) for miners (surface and underground coal, metal, and nonmetal mines): Full-shift limit = 0.1 fiber/cm³ (8-h time-weighted average); excursion limit = 1 fiber/cm³ (30-min sample).

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Ceiling concentration = 1 fiber/cm³ (excursion limit) as averaged over a sampling period of 30 min. Permissible exposure limit (PEL) = 0.1 fiber/cm³ for fibers longer than 5 μm having a length-to-diameter ratio of at least 3 to 1.

Comprehensive standards for occupational exposure to asbestos have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 respirable fiber/cc (cm³).

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

Recommended exposure limit (REL) = 0.1 fiber/cm³ (fibers longer than 5 μm).

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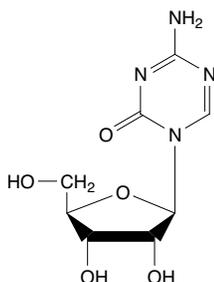
Azacitidine

CAS No. 320-67-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 5-azacytidine, 5-aza-C, or Vidaza (a registered trademark of Celgene Corporation)



Carcinogenicity

Azacitidine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to azacitidine by injection caused tumors at several different tissue sites in mice and rats. Intraperitoneal injection of azacitidine caused cancer of the hematopoietic system (lymphocytic or histiocytic lymphoma or granulocytic leukemia or sarcoma) in female mice and skin and lung tumors in mice of both sexes. Prenatal exposure of mice to azacitidine caused leukemia, lymphoma, and tumors of the lung and liver (NCI 1978, Luz and Murray 1988, IARC 1990). In male rats, intraperitoneal injection of azacitidine caused skin cancer (squamous-cell carcinoma) and tumors of the testis (interstitial-cell neoplasia) (IARC 1990).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to azacitidine.

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study, partially hepatectomized male rats were administered *N*-nitrosodiethylamine followed by chronic administration of azacitidine by intraperitoneal injection. The incidence of liver tumors and the combined incidence of skin and lung tumors were increased; all surviving rats developed hyperplastic liver nodules (Carr *et al.* 1988, IARC 1990).

Azacitidine in the absence of mammalian metabolic activation is genotoxic in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* test systems. It caused DNA damage and base-pair substitution mutations (but not frame-shift mutations) in prokaryotic systems and mitotic recombination, gene conversion, chromosomal aberrations, and gene mutations in somatic and germ

cells of lower eukaryotes (yeast, fruit flies, and plants). In cultured rodent cells, azacitidine inhibited DNA synthesis and caused sister chromatid exchange, chromosomal aberrations, gene mutations (in some but not all studies), and morphological cell transformation. In cultured human cells, azacitidine caused DNA damage and gene mutations; studies on sister chromatid exchange and chromosomal aberrations gave conflicting results. Azacitidine did not cause dominant lethal mutations in male mice exposed *in vivo* (IARC 1990).

The carcinogenic or tumor-enhancing activity of azacitidine has been postulated to result directly or indirectly from its ability to inhibit DNA methylation (Harrison *et al.* 1983, Riggs and Jones 1983, Kerbel *et al.* 1984, 1986, Takenaga 1986, Glover and Leyland-Jones 1987, Glover *et al.* 1987, IARC 1990, Jones and Buckley 1990, Haaf 1995). Altered levels of DNA methylation can affect gene expression (Cedar 1988, IARC 1990, Fajkus *et al.* 1992, Velge *et al.* 1995), and hypomethylation is associated with the expression of genes that are normally silent or downregulated. DNA hypomethylation is somatically heritable, causing alterations in gene expression that are maintained in daughter cells as the affected cells proliferate (Holliday 2006). In pBOR-II-3 mice, which are transgenic for the interleukin-3 (IL-3) gene (expression of which is driven by a long-terminal repeat), injection of azacitidine increased the incidence of thymic lymphoma over that observed in nontransgenic controls. The authors concluded that increased expression of IL-3, resulting from demethylation of the transgene long-terminal repeat by azacitidine, was responsible for the increased incidence of lymphoma (Saavedra *et al.* 1996). There is no evidence to suggest that the mechanisms by which azacitidine causes tumors in experimental animals would not also operate in humans.

Properties

Azacitidine is a pyrimidine analogue of cytidine that exists at room temperature as a white crystalline powder (IARC 1990). It is soluble in warm and cold water, 0.1 N hydrochloric acid, 0.1 N sodium hydroxide, 35% ethanol, and dimethyl sulfoxide, and slightly soluble in acetone, chloroform, and hexane. Azacitidine is stable under normal temperatures and pressures (Akron 2009), but is very unstable in aqueous solution, breaking down to complex products within hours (IARC 1990). Its stability in aqueous solutions depends on pH; in neutral and alkaline solutions, it has a half-life of 4 hours, but in Ringer's solution (pH 6.2), its half-life is 65 hours (Glover and Leyland-Jones 1987). Physical and chemical properties of azacitidine are listed in the following table.

Property	Information
Molecular weight	244.2 ^a
Melting point	228°C to 230°C (decomposes) ^a
Log <i>K</i> _{ow}	-3.83 ^b
Water solubility	89 g/L at 25°C ^b
Vapor pressure	4.1 × 10 ⁻¹² mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Azacitidine is a cytostatic anticancer drug that has been used in the United States since 1970. (NCI 1978). One product containing azacitidine as the active ingredient has been approved by the U.S. Food and Drug Administration; it is available in 100-mg vials for subcutaneous injection (FDA 2009). Azacitidine is approved to treat chronic myelomonocytic leukemia and myelodysplastic syndromes. It is also used to treat acute myeloblastic leukemia, breast cancer, colon cancer, melanoma, and ovarian cancer (IARC 1990, Santini *et al.* 2001, Celgene 2010). Azacitidine is also used in clinical trials in combina-

tion with other antineoplastic agents, such as vincristine, prednisone, vinblastine, cytarabine, or amsacrine (IARC 1990).

Production

Azacitidine may be produced synthetically or isolated from the bacterium *Streptovorticillium ladakanus* (IARC 1990). In 2009, azacitidine was available from 22 suppliers worldwide, including 15 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of azacitidine were found.

Exposure

The primary route of human exposure to azacitidine is intravenous or intramuscular injection in patients receiving anticancer therapy. Daily doses are 40 to 750 mg/m² of body surface. The typical treatment regimen starts with a dose of 75 mg/m² daily for one week of every four-week period (IARC 1990, Riley and DeRuiter 2005); the dose may be increased to 100 mg/m² as needed and if side effects are tolerable. In 2009, 80 clinical trials using azacitidine (alone or in combination with other drugs) for treatment of several types of cancer were in progress or recently completed (ClinicalTrials 2009). Occupational exposure could occur among health professionals and support staff (including custodians) by dermal contact, inhalation, or accidental ingestion during drug preparation or administration or cleanup of medical waste, including disposal of excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,069 health-services workers, including 698 women, potentially were exposed to azacitidine (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Azacitidine is regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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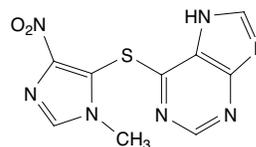
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Azathioprine

CAS No. 446-86-6

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Azathioprine is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Two large prospective epidemiological studies reported high incidences of non-Hodgkin's lymphoma, skin cancer (squamous-cell carcinoma), connective-tissue tumors (mesenchymal tumors), and cancer of the liver, bile ducts, or gallbladder (hepatobiliary carcinoma) in kidney-transplant patients, who are treated almost routinely with azathioprine and prednisone. Other patients treated with azathioprine (e.g., patients with rheumatoid arthritis, systemic lupus and other collagen disorders, inflammatory bowel disease, and certain skin and renal diseases) also had an increased, although lower,

risk of the same cancers as seen in the transplant patients. Rheumatoid arthritis is also a risk factor for non-Hodgkin's lymphoma (IARC 1981, 1982, 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of azathioprine from studies in experimental animals is limited. Cancer of the ear duct (squamous-cell carcinoma) was observed in rats orally exposed to azathioprine, and lymphoma was observed in mice exposed to azathioprine by intraperitoneal, subcutaneous, or intramuscular injection. The International Agency for Research on Cancer (IARC 1981, 1982, 1987) considered these results to be inconclusive because of limitations in the study designs and inadequate reporting of these studies.

Properties

Azathioprine is a purine analogue and antimetabolite (an inhibitor of purine synthesis) that exists as pale-yellow crystals at room temperature. It is insoluble in water, very slightly soluble in ethanol and chloroform, sparingly soluble in dilute mineral acids, and soluble in dilute alkaline solutions. It is sensitive to oxidation and decomposes in strong alkali solutions (IARC 1981). Physical and chemical properties of azathioprine are listed in the following table.

Property	Information
Molecular weight	277.3 ^a
Melting point	decomposes at 243°C to 244°C ^a
Log K_{ow}	0.1 ^a
Water solubility	0.272 g/L at 25°C ^b
Vapor pressure	2.41×10^{-12} mm Hg at 25°C ^b
Dissociation constant (pK_a)	8.2 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Azathioprine is an immunosuppressive agent, generally used in combination with a corticosteroid to prevent rejection following allogeneic kidney transplants (i.e., from genetically different donors) and to manage severe cases of rheumatoid arthritis in adults when other treatments have failed. It may also be used following transplantation of other organs and as a second-line treatment for a variety of immunological diseases, such as systemic lupus erythematosus, autoimmune hemolytic anemia, chronic active hepatitis, ulcerative colitis, Crohn's disease, and myasthenia gravis (IARC 1981, IPCS 1996, HSDB 2009).

Production

Azathioprine was first produced commercially in the United States in 1970 and was manufactured by one U.S. company (IARC 1981). In 2009, no U.S. producers of azathioprine were identified (SRI 2009), but it was available from at least nine U.S. suppliers (ChemSources 2009), and five U.S. pharmaceutical companies produced drugs approved by the U.S. Food and Drug Administration containing azathioprine as the active ingredient (FDA 2009). No data on U.S. imports or exports of azathioprine were found.

Exposure

The routes of exposure to azathioprine during medical treatment are ingestion and intravenous injection. Kidney-transplant patients and adults with severe cases of rheumatoid arthritis or other immunological diseases may be treated with azathioprine (IARC 1981). Azathioprine is available in 25-, 50-, 75-, and 100-mg tablets and in injectable form as the sodium salt in 100-mg vials (FDA 2009). The usual dose is 3 to 5 mg/kg of body weight daily for kidney transplant patients, which may be reduced to 1 to 3 mg/kg for maintenance. For rheuma-

toid arthritis, the initial dose is 1 mg/kg per day, and the dose may be increased to 2.5 mg/kg per day (RxList 2009). In 2008, sales of generic forms of azathioprine totaled \$53 million (Drug Topics 2009a). Azathioprine was not among the 200 most-prescribed generic drugs in 2008 (Drug Topics 2009b).

Occupational exposure to azathioprine may occur via inhalation of dust during its manufacture, formulation, and packaging. In a study at a pharmaceutical plant in South Africa, the highest median concentrations of azathioprine dust measured were 0.26 mg/m³ in the breathing zone and 0.07 mg/m³ in personal air samples (Jeebhay *et al.* 1993). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,849 workers, including 880 women, potentially were exposed to azathioprine (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Azathioprine is a prescription drug subject to labeling and other requirements.

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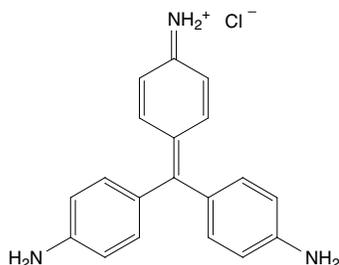
Basic Red 9 Monohydrochloride

CAS No. 569-61-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as C.I. basic red monohydrochloride, C.I. 42500, or pararosaniline hydrochloride



Carcinogenicity

Basic red 9 monohydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to basic red 9 monohydrochloride caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral administration of basic red 9 monohydrochloride caused liver cancer (hepatocellular carcinoma) in mice of both sexes and in male rats. In rats of both sexes, it caused cancer of the Zymbal gland (carcinoma), benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma), and benign skin tumors (fibroma). It also caused benign and malignant skin tumors (sebaceous adenoma, trichoepithelioma, and squamous-cell carcinoma) in male rats and benign adrenal-gland tumors (pheochromocytoma) in female mice. Other tumors possibly resulting from oral exposure were mammary-gland tumors in female rats and tumors of the hematopoietic system in female mice. Subcutaneous injection of basic red 9 monohydrochloride caused cancer at the injection site (sarcoma) in rats of unspecified sex (IARC 1974, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to basic red 9 monohydrochloride. Evidence for the possible carcinogenicity of basic red 9 monohydrochloride in humans comes from an epidemiological study in which the incidence of urinary-bladder tumors was elevated among workers involved in the manufacture of magenta dye, of which basic red 9 monohydrochloride is a component (IARC 1974). However, it is not possible to determine whether the increased incidence of cancer in magenta workers was attributable to exposure to magenta or to one or more of its intermediates and impurities, such as *o*-toluidine or aniline.

Since basic red 9 monohydrochloride was listed in the *Fifth Annual Report on Carcinogens*, the International Agency for Research on Cancer has reaffirmed that the evidence for carcinogenicity in humans is inadequate for magenta and basic red 9 monohydrochloride and sufficient for the manufacture of magenta (Baan *et al.* 2008).

Properties

Basic red 9 monohydrochloride is a triphenylmethane dye that is a colorless to red or dark-green crystalline powder at room tempera-

ture. It is slightly soluble in water and ether and soluble in ethanol, methanol, and ethylene glycol methyl ether (HSDB 2009). It is stable under normal temperatures and pressures, but may decompose if heated (Akron 2009). Physical and chemical properties of basic red 9 monohydrochloride are listed in the following table.

Property	Information
Molecular weight	323.8 ^a
Melting point	268°C to 270°C (decomposes) ^a
Log K_{ow}	0.21 ^a
Water solubility	3 g/L at 25°C ^b
Vapor pressure	9.26×10^{-10} mm Hg ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Basic red 9 monohydrochloride can be used to make C.I. solvent blue 23 and is a component of magenta dye (C.I. 42510). The Biological Stain Commission has determined that magenta must contain at least 50% C.I. basic red 9 in order to perform satisfactorily as a component of nutrient agar used in biological testing. Basic red 9 monohydrochloride is also used as a biological stain and as a dye for textiles (silks and acrylics), leather, fur, paper, carbon paper, plastics, glass, waxes, polishes, soaps, cosmetics, drugs, toilet sanitary preparations, automobile antifreeze solutions, anodized aluminum, high-speed photoduplicating inks, photo-imaging systems, and ink-jet computer printers (NTP 1986, IARC 1993, HSDB 2009).

Production

Two U.S. companies produced over 900 kg (2,000 lb) of C.I. basic red 9 in 1972, over 450 kg (1,000 lb) in 1975, and between 1 million and 10 million pounds in 1977 (NTP 1986, HSDB 2009). In 2009, no commercial producers of basic red 9 monohydrochloride were identified worldwide; however, 14 suppliers were identified, including 12 U.S. suppliers (ChemSources 2009). In 1974, the United States imported 2,000 kg (4,410 lb) of basic red 9 (HSDB 2009); no more recent data on U.S. exports or imports were found.

Exposure

The routes of potential human exposure to basic red 9 monohydrochloride are dermal contact, inhalation, and ingestion. Laboratory personnel who use and handle basic fuchsin dye might be exposed to basic red 9 monohydrochloride (HSDB 2009). Exposure might also occur through its use in magenta used in photoduplicating inks, photo-imaging systems, and ink-jet computer printers. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 907 workers (mostly from the Food and Kindred Products and Health Services industries), including 733 women, potentially were exposed to basic red 9 monohydrochloride (NIOSH 1990).

Regulations and Guidelines

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

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Benzene

CAS No. 71-43-2

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Benzene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Case reports and case series have reported leukemia (mostly acute myelogenous leukemia, also known as acute myeloid or myelocytic leukemia) in individuals exposed to benzene. The strongest epidemiological evidence that benzene causes cancer is from several cohort studies in various industries and geographical locations, which found that occupational exposure to benzene increased the risk of mortality from leukemia (mainly acute myelogenous leukemia). Case-control studies also reported that exposure to benzene increased the risk of leukemia, but the usefulness of these studies was limited by poorly defined exposures and mixed exposure patterns (IARC 1974, 1982, 1987).

Since benzene was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, numerous epidemiological studies of benzene exposure have been published. Some studies found that the risk of leukemia increased with increasing benzene exposure; increased risk of death from leukemia was very high in the groups with the highest exposure (IPCS 1993). Savitz and Andrews (1997) reviewed 18 community-based and 16 industry-based studies of benzene exposure and suggested that the evidence supported an association between benzene exposure and leukemia in general, rather than specifically with acute myelogenous leukemia. Most studies found that benzene exposure increased the risks of total lymphatic and hematopoietic cancer, total leukemia, and specific histologic types of leukemia, including chronic lymphocytic leukemia, as well as acute myelogenous leukemia. Little evidence was found for an association between benzene exposure and multiple myeloma or non-Hodgkin's lymphoma.

Cancer Studies in Experimental Animals

Studies in experimental animals, including many published after benzene was listed in the *First Annual Report on Carcinogens*, have

demonstrated that benzene causes cancer at numerous tissue sites in rodents. Oral exposure to benzene caused cancer of the Zymbal gland (carcinoma) in rats and mice of both sexes, cancer of the oral cavity (squamous-cell carcinoma) in rats of both sexes, malignant lymphoma and lung cancer (alveolar/bronchiolar carcinoma) in mice of both sexes, skin cancer (squamous-cell carcinoma) in male rats, benign tumors of the Harderian gland (adenoma) and cancer of the preputial gland (carcinoma) in male mice, and benign ovarian tumors and cancer of the mammary gland (carcinoma and carcinosarcoma) in female mice (NTP 1986, Huff *et al.* 1989). Inhalation exposure to benzene caused tumors at many tissue sites in rats and a tendency towards induction of lymphoid tumors in mice. Benzene administered by intraperitoneal injection caused benign lung tumors in male mice (IARC 1982, 1987). Dermal application of benzene caused benign skin tumors in transgenic mice carrying the *v-Ha-ras* oncogene, which increases their susceptibility to carcinogens (Blanchard *et al.* 1998, Spalding *et al.* 1999, French and Saulnier 2000). In heterozygous *p53*-deficient mice (with only one functional copy of the *p53* tumor-suppressor gene), benzene administered by stomach tube caused cancer (sarcoma) of head and neck, thoracic cavity, and subcutaneous tissue (French *et al.* 2001, Hulla *et al.* 2001).

Properties

Benzene is the primary aromatic compound. It exists at room temperature as a clear, colorless-to-yellow liquid with an aromatic odor. It is only slightly soluble in water, but it is miscible with alcohol, ether, chloroform, carbon disulfide, acetone, oils, carbon tetrachloride, glacial acetic acid, and most other organic solvents. Benzene is highly flammable (Akron 2009). Physical and chemical properties of benzene are listed in the following table.

Property	Information
Molecular weight	78.1
Specific gravity	0.8787 at 15°C/4°C
Melting point	5.5°C
Boiling point	80.1°C
Log K_{ow}	2.13
Water solubility	1.79 g/L at 25°C
Vapor pressure	94.8 mm Hg at 25°C
Vapor density relative to air	2.8

Source: HSDB 2009.

Use

Benzene is used primarily as a solvent in the chemical and pharmaceutical industries, as a starting material and intermediate in the synthesis of numerous chemicals, and in gasoline. As a raw material, it is used in the synthesis of ethylbenzene (used to produce styrene) (53%), cumene (used to produce phenol and acetone) (22%), cyclohexane (12%), nitrobenzene (used to produce aniline and other chemicals) (5%), detergent alkylate (linear alkylbenzene sulfonates) (3%), and chlorobenzenes and other products (5%). Benzene is used as an additive in gasoline, but it also is present naturally in gasoline, because it occurs naturally in crude oil and is a by-product of oil-refining processes. The percentage of benzene in unleaded gasoline is approximately 1% to 2% by volume (ATSDR 1997, HSDB 2009).

Production

Benzene has been produced commercially from coal since 1849 and from petroleum since 1941. Since 1959, the major U.S. source of benzene has been petroleum (IARC 1989). In 1994, benzene ranked 17th in production volume among chemicals produced in the United States. U.S. production of benzene increased from 5.4 million metric tons (12.0 billion pounds) in 1992 to 7.2 million metric tons (15.8

billion pounds) in 2002, an average increase of 2.8% per year (CEN 2003). Annual production during this period was highest in 2000, at 8.1 million metric tons (17.8 billion pounds). In 2009, 59 U.S. manufacturers (SRI 2009) and 24 U.S. suppliers of benzene were identified (ChemSources 2009). In 2002, U.S. imports of benzene totaled over 4 billion liters (1.1 billion gallons), which greatly exceeded exports of 6 million liters (1.6 million gallons). This trend continued in 2008, when 3.9 billion liters (1.03 billion gallons) was imported and 49.6 million liters (13.1 million gallons) was exported (USITC 2009).

Exposure

The primary route of human exposure to benzene is inhalation of ambient air. Benzene is present in the atmosphere both from natural sources, which include forest fires and oil seeps, and from industrial sources, which include automobile exhaust, industrial emissions, and fuel evaporation from gasoline filling stations. Benzene has been measured in outdoor air at various U.S. locations at concentrations ranging from 0.02 ppb (0.06 $\mu\text{g}/\text{m}^3$) in a rural area to 112 ppb (356 $\mu\text{g}/\text{m}^3$) in an urban area. The maximum 24-hour average concentrations of benzene reported for four U.S. cities in 2004 were 1.1 ppb (3.5 $\mu\text{g}/\text{m}^3$) for St. Louis, Missouri, 2.7 ppb (8.6 $\mu\text{g}/\text{m}^3$) for Chicago, Illinois, 2.9 ppb (9.3 $\mu\text{g}/\text{m}^3$) for Los Angeles, California, and 73.5 ppb (234.8 $\mu\text{g}/\text{m}^3$) for Houston, Texas (Clements *et al.* 2006). Exposure to benzene is highest in areas of heavy motor vehicle traffic and around gasoline filling stations. Based on an average benzene concentration of 12.5 ppb (40 $\mu\text{g}/\text{m}^3$) in the air and exposure of 1 hour per day, daily benzene intake from driving or riding in a motor vehicle is estimated to be 40 μg . Exposure is greater among people who spend significant time in motor vehicles in areas of congested traffic. In addition, pumping of gasoline can be a significant source of benzene exposure; for an individual spending 70 minutes per year pumping gasoline, daily benzene intake is estimated to be 10 μg (ATSDR 1997).

The general population can also be exposed to benzene by inhaling air containing tobacco smoke, drinking contaminated water, or eating contaminated food. About half of the total national exposure to benzene comes from cigarette smoke. The median level of benzene was 2.2 ppb (7 $\mu\text{g}/\text{m}^3$) in 185 homes without smokers and 3.3 ppb (10.5 $\mu\text{g}/\text{m}^3$) in 343 homes with one or more smokers. Amounts of benzene measured per cigarette ranged from 5.9 to 75 μg in mainstream smoke and from 345 to 653 μg in sidestream smoke. Benzene has been detected in fruits, vegetables, nuts, dairy products, eggs, and fish. In a 1992 survey of more than 50 foods, benzene concentrations in foods containing both benzoate and ascorbate food additives ranged from less than 1 to 38 ppb (< 3 to 120 $\mu\text{g}/\text{m}^3$) (ATSDR, 1997). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of benzene decreased from 34 million pounds in 1988 to 6 million pounds in 2001, when 5 million pounds was released to air and 19,000 lb to water. In 2007, 775 facilities released 6.3 million pounds of benzene (TRI 2009). Benzene levels in water in the vicinity of four manufacturing facilities using or producing benzene ranged from less than 1 to 179 ppb (< 3 to 569 $\mu\text{g}/\text{m}^3$) (ATSDR, 1997).

Occupational exposure may occur during production of benzene or use of substances containing it. In the vulcanization step of tire manufacturing, benzene was measured at concentrations of up to 27.2 mg/m^3 , resulting in an estimated daily intake of 0.0045 mg/kg of body weight for workers (Durmusoglu 2007). The National Occupational Health Survey (conducted from 1972 to 1974) estimated that 147,600 U.S. workers potentially were exposed to benzene (NIOSH 1976), and the National Occupational Exposure Survey (conducted

from 1981 to 1983) estimated that about 272,000 workers, including 143,000 women, potentially were exposed to benzene (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Comprehensive regulations have been established for safe transport of benzene on ships and barges.

Consumer Product Safety Commission (CPSC)

Products containing 5% or more by weight of benzene are considered hazardous and require special labeling.

Solvents for paints or other surface-coating materials containing 10% or more by weight of benzene require special packaging.

Department of Transportation (DOT)

Benzene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Comprehensive regulations have been developed to control benzene levels in gasoline and benzene emissions from motor vehicles.

Mobile Source Air Toxics: Beginning in 2011, refiners must meet an annual average gasoline benzene content standard of 0.62% by volume (vol%) on all gasoline; by 2012, a maximum benzene content of 1.3 vol% may not be exceeded.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 2.2 $\mu\text{g}/\text{L}$; based on fish or shellfish consumption only = 51 $\mu\text{g}/\text{L}$.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L .

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of benzene = U019, F005, F024, F025, F037, F038, K085, K104, K105, K141, K142, K143, K144, K145, K147, K151, K159, K169, K171, K172.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L .

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L .

Residues of benzene used as a solvent in producing modified hop extract shall not exceed 1.0 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Acceptable peak exposure = 50 ppm (maximum duration = 10 min) for select industries.

Ceiling concentration = 25 ppm for select industries.

Permissible exposure limit (PEL) = 1 ppm; = 10 ppm for select industries.

Short-term exposure limit (STEL) = 5 ppm.

Comprehensive standards for occupational exposure to benzene have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 2.5 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 500 ppm.

Short-term exposure limit (STEL) = 1 ppm.

Recommended exposure limit (time-weighted-average workday) = 0.1 ppm.

Listed as a potential occupational carcinogen.

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Benzidine and Dyes Metabolized to Benzidine

Introduction

Benzidine was first listed in the *First Annual Report on Carcinogens* (1980), and dyes metabolized to benzidine were first listed as a class in the *Ninth Report on Carcinogens* (2000). The profiles for benzidine and dyes metabolized to benzidine, which are listed (separately) as *known to be human carcinogens*, follow this introduction.

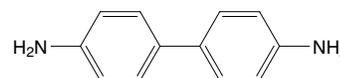
Benzidine

CAS No. 92-87-5

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as 4,4'-diaminobiphenyl



Carcinogenicity

Benzidine is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous epidemiological studies (case reports and cohort studies) of workers in various geographical locations have reported a strong association between occupational exposure to benzidine and urinary-bladder cancer. Moreover, epidemiological data suggest that urinary-bladder cancer incidence has decreased since measures to limit benzidine exposure were instituted. A few studies have evaluated exposure to benzidine alone; however, in many studies, workers were co-exposed to other chemicals. Some studies have suggested that the risk of urinary-bladder cancer increases with increasing length of exposure to benzidine (IARC 1972, 1982, 1987). Since benzidine was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, some, but not all, studies have reported an association between benzidine exposure and cancer at other tissue sites (i.e., liver, kidney, central nervous system, oral cavity, larynx, esophagus, bile duct, gallbladder, stomach, and pancreas); the evidence for an association with benzidine is more limited for cancer at these tissue sites than for urinary-bladder cancer (Choudhary 1996).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of benzidine from studies in experimental animals. Oral exposure to benzidine caused mammary-gland cancer in female rats, liver cancer in mice and hamsters, and urinary-bladder cancer in dogs. When administered by subcutaneous injection, benzidine caused Zymbal-gland tumors in rats and liver tumors in mice, and when administered by intraperitoneal injection, it caused Zymbal-gland and mammary-gland tumors in rats (IARC 1982, 1987).

Studies on Mechanisms of Carcinogenesis

Benzidine is metabolized by cytochrome P450 enzymes (via N-oxidation) to form electrophilic compounds that can bind covalently to DNA (Choudhary 1996). Benzidine caused mutations in bacteria and plants, but gave conflicting results in cultured rodent

cells. It also caused many other types of genetic damage in various test systems, including yeast, cultured human and other mammalian cells, and rodents exposed *in vivo*. The damage included mitotic gene conversion (in yeast), micronucleus formation, DNA strand breaks, unscheduled DNA synthesis, cell transformation, chromosomal aberrations, sister chromatid exchange, and aneuploidy (IARC 1987). Workers exposed to benzidine and or benzidine-based dyes had higher levels of chromosomal aberrations in their white blood cells than did unexposed workers (Choudhary 1996).

Properties

Benzidine is a biphenyl amine that exists at room temperature as a white to slightly reddish crystalline powder (ATSDR 2001). It is slightly soluble in cold water, more soluble in hot water, and readily soluble in less-polar solvents, such as diethyl ether and ethanol. It darkens on exposure to air and light (Akron 2009). Physical and chemical properties of benzidine are listed in the following table.

Property	Information
Molecular weight	184.2 ^a
Specific gravity	1.250 at 20°C/4°C ^a
Melting point	120°C ^a
Boiling point	401°C ^a
Log K_{ow}	1.34 ^a
Water solubility	0.322 g/L at 25°C ^a
Vapor pressure	8.98×10^{-7} mm Hg at 25°C ^b
Vapor density relative to air	6.36 ^a
Dissociation constant (p <i>K</i> _a)	4.3 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Benzidine has been used for over a century as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds (IARC 1982). In the past, benzidine also was used in clinical laboratories for detection of blood, as a rubber compounding agent, in the manufacture of plastic films, for detection of hydrogen peroxide in milk, and for quantitative determination of nicotine. Most of these uses have been discontinued because of concerns about benzidine's potential carcinogenicity. Some dyes that may contain benzidine as an impurity are still used as stains for microscopy and similar laboratory applications (ATSDR 2001).

Production

Benzidine is no longer manufactured for commercial sale in the United States (ATSDR 2001). All large-scale production was discontinued in 1976, and only relatively small quantities remain available for use in diagnostic testing. All benzidine production must be for captive consumption (in-house use) and take place in closed systems under stringent workplace controls. Estimated U.S. benzidine production in 1983 was only 500 lb (possibly excluding some captive production), compared with 10 million pounds in 1972 (ATSDR 2001). In 2009, no U.S. manufacturers of benzidine were identified (SRI 2009), but it was available from 13 U.S. suppliers (ChemSources 2009). Benzidine has not been imported into the United States in recent years. In 1980, the last year for which an estimate was found, U.S. imports of benzidine totaled 8,900 lb (ATSDR 2001). No data on U.S. exports of benzidine were found.

Exposure

Because benzidine may be produced only for captive consumption, its direct release into the environment is expected to be low. However, accidental releases from closed systems potentially could result in exposure of the general population through inhalation, ingestion,

or dermal contact (ATSDR 2001). According to EPA's Toxics Release Inventory, environmental releases of benzidine were 16 lb in 1993, 250 lb in 1994, and 2 lb in 1999. Releases peaked in 2001, when 532 lb was released (300 lb to surface water and most of the rest to an off-site landfill). In 2007, two facilities released a total of 16 lb of benzidine (6 lb to air and 10 lb to a hazardous-waste landfill) (TRI 2009). In the past, benzidine might have been released into wastewaters and sludges. Because benzidine is moderately persistent in the environment, exposure of populations living near former benzidine or benzidine-dye manufacturing or waste-disposal sites may still be of concern. Benzidine has been identified in 28 of 1,585 hazardous-waste sites proposed for inclusion on the U.S. Environmental Protection Agency's National Priorities List; however, it is not known how many sites were evaluated for benzidine. In 1990, benzidine was detected in groundwater at a hazardous-waste site (the former location of a large dye manufacturer) at concentrations of 240 µg/L on site and 19 µg/L off site (ATSDR 2001).

Benzidine-based dyes may still be imported into the United States, and microbial degradation of these dyes may release free benzidine into the environment (ATSDR 2001). The U.S. Food and Drug Administration limits the benzidine content in food colorants to 1 ppb; however, other impurities in synthetic coloring agents may be metabolized to benzidine after ingestion.

Before Occupational Safety and Health Administration regulations were adopted to limit occupational exposure to benzidine (starting in 1974), benzidine and its derivatives were manufactured and used in open systems that permitted release of benzidine into workplace air. Air concentrations of benzidine measured in a benzidine manufacturing plant ranged from 0.007 to 17.6 mg/m³, and levels in the urine of exposed workers ranged from 1 to 112 µg/L (ATSDR 2001). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,554 workers, including 426 women, potentially were exposed to benzidine (NIOSH 1990). Benzidine is available in limited quantities for use as a research chemical and may be present as a trace impurity in stains used by medical or laboratory technicians. Others potentially exposed to benzidine include workers involved in its production in closed systems and workers at hazardous-waste sites where benzidine is present (ATSDR 2001).

Regulations

Department of Transportation (DOT)

Benzidine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.000086 µg/L; based on fish or shellfish consumption only = 0.00020 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of benzidine = U021.

Benzidine is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

The color additives FD&C yellow no. 5 and yellow no. 6 and D&C red no. 33 may contain benzidine at maximum levels that range from 1 to 20 ppb.

The color additive Ext. D&C yellow no. 1 is banned, because there is no assurance that it will not produce benzidine from the decomposition of a subsidiary reaction product.

Mine Safety and Health Administration

To control airborne exposure, benzidine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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Dyes Metabolized to Benzidine (Benzidine Dye Class)

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Dyes that are metabolized to benzidine are *known to be human carcinogens* based on the following evidence: (1) benzidine is known to be a human carcinogen, (2) metabolism of benzidine-based dyes results in the release of free benzidine in humans and in all experimental animal species studied, and (3) benzidine exposure from exposure to benzidine-based dyes is equivalent to exposure to equimolar doses of benzidine.

Studies on Mechanisms of Carcinogenesis

Benzidine was one of the first chemicals for which an association between occupational exposure and increased cancer risk was recognized. Industrial exposure to benzidine was first associated with urinary-bladder cancer in the early 1920s. Benzidine was listed as

known to be a human carcinogen in the *First Annual Report on Carcinogens* (1980). The evidence supporting its listing is summarized in the profile for benzidine, above.

Benzidine was first synthesized in 1845, and the first benzidine-based dye, Congo red, was prepared in 1884. A wide spectrum of colors can be achieved by varying the dye molecules' chromophores, which are linked to benzidine by an azo linkage (–N=N–). Similar or different chromophores may be linked at each amino (NH₂) group of the benzidine molecule to form various bisazobiphenyl dyes. Regardless of the chromophore(s) involved, the azo linkages of all benzidine-based dyes are essentially chemically equivalent; easily formed, they also are easily broken by chemical or enzymatic reduction to form free benzidine and free chromophore(s). Benzidine-based dyes were shown to be metabolized to free benzidine in rats, dogs (Lynn *et al.* 1980), hamsters (Nony *et al.* 1980), and rhesus monkeys, probably by bacteria in the gastrointestinal tract (Rinde and Troll 1975). Lowry *et al.* (1980) concluded that the amount of benzidine and its metabolites detected in urine of exposed workers could not be accounted for by the minute amounts of free benzidine in the dyes to which they were exposed, and therefore that humans also metabolize benzidine-based dyes to free benzidine. Lynn *et al.* (1980) found that in rats and dogs, each benzidine-based dye studied was reduced to yield an amount of free benzidine equal to that observed following an equimolar dose of benzidine.

Cancer Studies in Experimental Animals

All three benzidine-based dyes that have been tested caused cancer in rodents after oral exposure for 13 weeks (NCI 1978, IARC 1982). C.I. direct black 38 caused liver cancer in rats and mice, mammary-gland cancer in mice, and colon and urinary-bladder cancer in rats. C.I. direct blue 6 caused liver cancer in rats, and C.I. direct brown 95 caused neoplastic nodules in the liver and one malignant liver tumor in rats. Based on these data, the International Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of technical-grade C.I. direct black 38, technical-grade C.I. direct blue 6, and technical-grade C.I. direct brown 95 in experimental animals.

Cancer Studies in Humans

Because benzidine workers exposed to benzidine-based dyes typically have been co-exposed to benzidine, it has been difficult to clearly establish the carcinogenicity of benzidine-based dyes in epidemiological studies. In studies of Chinese workers who remained in the same jobs for many years, the incidence of urinary-bladder cancer was elevated in workers who had been exposed almost exclusively to benzidine-based dyes (You *et al.* 1990) and in workers exposed to both benzidine and benzidine-based dyes (Bi *et al.* 1992). However, neither report adequately documented levels of exposure to either benzidine or the dyes. IARC (1982) concluded that the epidemiological data were inadequate to evaluate the carcinogenicity of individual benzidine dyes to humans, but that taken together with the presence of benzidine in the urine of exposed workers, they provided sufficient evidence that occupational exposure to benzidine-based dyes increased the risk of cancer in humans.

Properties

All benzidine-based dyes have the characteristic diazotized benzidine nucleus (the structure of benzidine is shown in the profile above) but differ with respect to the chemical groups attached at the diazo linkages. Most of the dyes in this class contain two or three azo groups, but they can contain more. They all exist as colored powders (in a wide range of hues) at room temperature and have negligible vapor

pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. Benzidine-based dyes are relatively stable in air and in solution at ambient temperatures but degrade in aqueous solution at high temperatures, particularly in the presence of iron. Impurities, such as benzidine, 4-aminobiphenyl, and 2,4-diaminobenzene, may be present in these dyes as a result of thermal or enzymatic decomposition (NIOSH 1980). There are no rigid chemical specifications for benzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer (IARC 1982). Various dyes are also mixed together to produce particular colors; therefore, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

Benzidine-based dyes were used primarily to color textiles, leather, and paper products and also in the petroleum, rubber, plastics, wood, soap, fur, and hair-dye industries. About 40% was used to color paper, 25% to color textiles, 15% to color leather, and 20% for diverse applications. By the mid 1970s, most manufacturers started phasing out the use of benzidine-based dyes and replacing them with other types of dyes (NIOSH 1980). More than 300 benzidine-based dyes are listed in the *Colour Index*, including 18 commercially available in the United States. Access to these dyes for home use is no longer permitted in the United States; however, some dyes (particularly direct browns, greens, and blacks) were available as consumer products in the 1970s (ATSDR 2001).

Production

Commercial quantities of benzidine-based dyes were produced in the United States starting no later than 1914, and total U.S. production reached 14 million kilograms (31 million pounds) in 1948 (IARC 1982). In 1974, nine U.S. manufacturers produced benzidine-based dyes, but by 1979, only one manufacturer remained, producing 17 benzidine-based dyes. Domestic production was about 2.9 million kilograms (6.4 million pounds) in 1976, but dropped to about 780,000 kg (1.7 million pounds) in 1978. Direct black 38 accounted for about 48% of U.S. production in 1978, followed by direct blue 2 (12.8%) and direct green 6 (6.4%) (NIOSH 1980). As of 2009, several benzidine-based dyes still had U.S. suppliers, including direct red 28 (28 suppliers), direct black 38 (12 suppliers), direct blue 6 (5 suppliers), direct green 6 (3 suppliers), direct brown 95 (3 suppliers), direct brown 2 (1 supplier), and direct blue 2 (1 supplier) (ChemSources 2009). However, these dyes are no longer used or marketed in significant quantities in the United States (ATSDR 2001). U.S. imports of benzidine-based dyes increased from 272,000 kg (600,000 lb) in 1976 to 730,000 kg (1.6 million pounds) in 1978 (NIOSH 1980) and declined to 213,000 kg (469,000 lb) in 1979. Benzidine-based dyes may still be imported into the United States, but no data on the amounts were found (ATSDR 2001).

Exposure

The primary routes of potential exposure to benzidine-based dyes are inhalation and accidental ingestion; however, dermal absorption also can occur. The potential for exposure has declined since the late 1970s, as benzidine-based dyes were removed from both industrial and consumer markets and replaced with other types of dyes. Since 1980, use of mixtures containing benzidine at concentrations of 0.1% or more is permitted only in closed systems; all workers must observe special precautions to reduce exposure, and strict procedures must be followed to transport such materials. Nevertheless, acciden-

tal releases of these dyes could lead to some occupational and environmental exposure (IARC 1982, ATSDR 2001).

In the past, environmental exposure to benzidine-based dyes potentially occurred in the vicinity of dye and pigment plants or waste-disposal sites. According to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009), no environmental releases of benzidine-based dyes have been reported since 1989, when 750 lb of direct black 38 was released. The National Occupational Hazard Survey (NOHS, conducted from 1972 to 1974) estimated that 79,200 workers in 63 occupations (primarily the Dye Manufacturing, Textile Dyeing, Printing, Paper, and Leather industries) potentially were exposed to benzidine-based dyes (NIOSH 1976). In a Special Occupational Hazard Review for benzidine-based dyes, the National Institute for Occupational Safety and Health identified 236 benzidine-based dyes and stated that occupational exposure to such dyes had decreased since the NOHS. Of the benzidine-based dyes specifically mentioned in this profile, four (direct blue 6 tetrasodium salt and the disodium salts of direct black 38, direct brown 95, and direct red 28) were included in the National Occupational Exposure Survey (conducted from 1981 to 1983); the estimated numbers of potentially exposed workers ranged from 830 for direct brown 95 disodium salt to 11,374 for direct black 38 disodium salt (NIOSH 1990). Although no current estimate of occupational exposure to benzidine-based dyes was found, the number of potentially exposed workers is expected to be much lower than in the past.

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: C.I. direct blue 6, C.I. direct blue 218, C.I. direct black 38, and C.I. direct brown 95 are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Benzidine-based dyes are considered potential occupational carcinogens, and it is recommended that worker exposure be reduced to the lowest feasible level.

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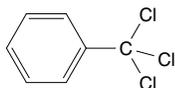
Benzotrichloride

CAS No. 98-07-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as 1-(trichloromethyl)benzene, α,α,α -trichlorotoluene, or benzoic trichloride



Carcinogenicity

Benzotrichloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to benzotrichloride by two routes of administration caused tumors at several different tissue sites in mice. When administered to female mice by stomach tube, benzotrichloride caused cancer of the forestomach (squamous-cell carcinoma) and of the lining of the lung (adenocarcinoma). Benzotrichloride applied to the skin of female mice caused lymphoma, cancer of the skin and lung (squamous-cell carcinoma), and cancer of the upper digestive tract (carcinoma of the lips, tongue, esophagus, and stomach) (IARC 1982a,b).

Since benzotrichloride was listed in the *Fourth Annual Report on Carcinogens*, additional studies in mice have been identified. Inhalation exposure of female mice to benzotrichloride caused benign and malignant lung and skin tumors (Yoshimura *et al.* 1986). In male and female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), benzotrichloride given by intraperitoneal injection caused benign lung tumors (adenoma) (Stoner *et al.* 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to benzotrichloride. However, epidemiological data provide limited evidence that employment in the production of chlorinated toluenes, which involves potential exposure to benzotrichloride and other α -chlorinated toluenes, may increase the risk of cancer (IARC 1982a,b). The evidence includes (1) six case reports of respiratory-tract cancer in young benzoyl chloride production workers, including three nonsmokers, who potentially were exposed to benzotrichloride and (2) excess deaths from lung cancer in two cohorts of workers potentially exposed to benzotrichloride and other chlorinated toluenes (IARC 1982a,b). Subsequent studies reviewed by the International

Agency for Research on Cancer (IARC 1999) have also reported excesses of respiratory-system cancer in workers with mixed exposure to benzotrichloride and other chlorinated toluenes (Sorahan *et al.* 1983, Wong *et al.* 1988, Sorahan and Cathcart 1989).

Properties

Benzotrichloride is a chlorinated aromatic hydrocarbon. At room temperature, it is a clear, colorless to yellow, oily liquid with a penetrating odor. It is practically insoluble in water, but it is soluble in diethyl ether, benzene, and ethanol (HSDB 2009). It is unstable and hydrolyzes in the presence of moisture (IARC 1982b). Physical and chemical properties of benzotrichloride are listed in the following table.

Property	Information
Molecular weight	195.5 ^a
Specific gravity	1.38 at 20°C/4°C ^a
Melting point	-5°C ^a
Boiling point	221°C at 760 mm Hg ^a
Log K_{ow}	2.92 ^a
Water solubility	53 mg/L at 5°C ^b
Vapor pressure	0.414 mm Hg at 25°C ^a
Vapor density relative to air	6.77 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Benzotrichloride is used extensively as a chemical intermediate in manufacturing processes. Its most important derivative is benzoyl chloride (IARC 1999). It has also been used as a dye intermediate in the preparation of eight dyes and pigments, including five that have been produced in commercial quantities in the United States. In addition, benzotrichloride has been used to make benzotrifluoride and hydroxybenzophenone ultraviolet-light stabilizers for plastics and in the production of ion-exchange resins, pharmaceuticals, and antimicrobial agents (IARC 1982b).

Production

In 2009, benzotrichloride was produced by 16 manufacturers worldwide (7 in India, 4 in Europe, 3 in China, 2 in East Asia, and none in the United States) (SRI 2009) and was available from 251 suppliers, including 14 U.S. suppliers (ChemSources 2009). U.S. imports of benzotrichloride were reported in a combined category with benzyl chloride. Imports in this category were between 562,000 and 1.2 million kilograms (1.2 million and 2.7 million pounds) from 1989 to 1997, increasing to a peak of 6.2 million kilograms (13.7 million pounds) in 2001 and declining to 3.2 million kilograms (7.1 million pounds) in 2004. During this period, U.S. exports of benzotrichloride were reported in the large category of "halogenated derivatives of aromatic hydrocarbons, not elsewhere specified or included" and ranged from a high of 65 million kilograms (144 million pounds) in 1996 to a low of 20 million kilograms (44 million pounds) in 2001 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of benzotrichloride between 1986 and 2006 ranged from 10 million to 50 million pounds (EPA 2004, 2009).

Exposure

The routes of potential human exposure to benzotrichloride are inhalation, ingestion, and dermal contact. The potential for exposure of the general population to benzotrichloride from industrial releases is expected to be low, because the chemical hydrolyzes rapidly in the presence of moisture and is degraded in the vapor phase in the at-

mosphere by reaction with photochemically produced hydroxyl radicals (IARC 1982b, HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of benzotrachloride in 1988 totaled 35,000 lb, of which 25,000 lb was released to air and 10,000 lb to off-site nonhazardous-waste landfills. Releases have since declined steadily and significantly. Since 2002, the small quantity of benzotrachloride not emitted to air (< 20 lb) has been sent to hazardous-waste landfills. In 2003, six facilities released 1,200 lb of benzotrachloride to air (TRI 2009). Benzotrachloride has been identified in surface waters at unreported concentrations (IARC 1982b).

Occupational exposure can occur if benzotrachloride is released in the work environment in liquid or vapor form during its manufacture or use as a chemical intermediate. Workers could potentially be exposed during the production, formulation, packaging, or application of products made with benzotrachloride or benzoyl chloride. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 171 male workers potentially were exposed to benzotrachloride (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Benzotrachloride is considered a hazardous material and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of substance is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Threshold planning quantity (TPQ) = 100 lb.

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of benzotrachloride = U023, K015, K149.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 0.1 ppm.

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Beryllium and Beryllium Compounds

CAS No. 7440-41-7 (Beryllium)

No separate CAS No. assigned for beryllium compounds as a class

Known to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as Be

Carcinogenicity

Beryllium and beryllium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans. Beryllium and beryllium compounds were first listed in the *Second Annual Report on Carcinogens* as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be human carcinogens* in the *Tenth Report on Carcinogens* in 2002.

Cancer Studies in Humans

Epidemiological studies indicate an increased risk of lung cancer in occupational groups exposed to beryllium or beryllium compounds (Steenland and Ward 1991, Ward *et al.* 1992), supporting the conclusion that beryllium and beryllium compounds are carcinogenic in humans. An association with lung cancer has consistently been observed in several occupational populations exposed to beryllium or beryllium compounds, with a relative risk of 1.2 to 1.6. Groups with greater exposure or longer time since first exposure show higher risks, which supports a cause-and-effect relationship. Acute beryllium pneumonitis, which is a marker for high exposure to beryllium, is associated with higher lung-cancer rates (with a relative risk as high as 2.3) (Steenland and Ward 1991). Although smoking could be a factor in the cancers observed in these studies, no evidence was found in any of the published epidemiological studies to indicate a difference in smoking habits between the groups of workers exposed to beryllium or beryllium compounds and the non-exposed workers in the control groups.

Cancer Studies in Experimental Animals

Beryllium and/or beryllium compounds caused tumors in several species of experimental animals, at two different tissue sites, and by several different routes of exposure. Beryllium metal and several beryllium compounds, including beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium hydroxide, beryllium sulfate tetrahy-

drate, and beryllium oxide, caused lung tumors in rats exposed by either inhalation for one hour or a single intratracheal instillation. Inhalation exposure to beryllium metal also caused lung tumors in *p53^{+/-}* transgenic mice (a strain with increased susceptibility to carcinogen-induced cancer). In rhesus monkeys, lung cancer was observed following inhalation exposure to beryllium sulfate (anaplastic carcinoma) or intrabronchial implantation of beryllium oxide. Bone cancer (osteosarcoma) was observed in rabbits exposed to beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate, or zinc beryllium silicate by intravenous injection or implantation into the bone (IARC 1993, Finch *et al.* 1996, 1998)

Studies on Mechanisms of Carcinogenesis

Beryllium compounds did not cause mutations in *Salmonella typhimurium*, but they did cause genetic damage in various cultured rodent cells (IARC 1993). The genotoxic effects of beryllium compounds may result from binding of ionic beryllium to nucleic acids, which can cause infidelity of DNA replication (Leonard and Lauwerys 1987).

Properties

Beryllium is a silver-gray to grayish-white group II metallic element with an atomic weight of 9.01, melting point of 1,287°C, boiling point of 2,970°C, and density of 1.85 at 20°C. It has a close-packed hexagonal crystal structure and has several unique chemical properties. It is the lightest of all solid and chemically stable substances and has a very high melting point, specific heat, heat of fusion, and strength-to-weight ratio. Beryllium is lighter than aluminum, but it is over 40% more rigid and approximately one-third more elastic than steel. It is insoluble in water but soluble in acids and alkalis. It has excellent electrical and thermal conductivity and is not magnetic. At ordinary temperatures, beryllium resists oxidation in air; however, a thin film of beryllium oxide forms on the surface, making it highly resistant to corrosion. In alloys, beryllium contributes hardness, strength, and high electrical and thermal conductivity and enhances resistance to corrosion, wear, and fatigue (IPCS 1990, IARC 1993, HSDB 2009).

Beryllium chloride occurs as white-to-colorless deliquescent crystals. It is highly soluble in water, alcohol, benzene, ether, chloroform, and carbon disulfide, and insoluble in ammonia and acetone. Beryllium fluoride occurs as a colorless amorphous mass that is readily soluble in water but only slightly soluble in alcohol. Beryllium hydroxide exists in three forms: a metastable tetragonal crystalline solid, a stable orthorhombic crystalline solid, and a slimy, gelatinous substance with a slightly basic pH. It is insoluble in water but soluble in acids and alkalis. Beryllium oxide occurs as a white powder or gel that is insoluble in hot water and soluble in acids, alkalis, and ammonium carbonate. Beryllium metaphosphate is a white porous powder or granular material that is insoluble in water. Beryllium orthophosphate is soluble in water and acetic acid. Beryllium sulfate occurs as colorless crystals; it is insoluble in cold water and alcohol but decomposes in hot water. Beryllium sulfate tetrahydrate occurs as colorless crystals that are soluble in water, practically insoluble in ethanol, and slightly soluble in concentrated sulfuric acid (IARC 1993, ATSDR 2002).

Beryl ore occurs as colorless, blue-green, yellow, or white transparent hexagonal crystals that are insoluble in acid. Beryllium-copper alloy usually contains 4.0% to 4.25% beryllium by weight. It has a melting point of 870°C to 980°C and produces toxic fumes of beryllium oxide upon heating. Beryllium-aluminum alloy may contain 20% to 60% beryllium (IARC 1993, ATSDR 2002).

Use

Beryllium's unique properties (as a light metal with a very high melting point) make it very useful in industry. In alloys, it increases ther-

mal and electrical conductivity and strength; addition of just 2% beryllium to copper forms alloys that are six times stronger than copper alone (IARC 1993). A 2010 U.S. Geological Survey Mineral Commodities Survey reported that based on sales revenues, nearly half of beryllium use was in computer and telecommunications products, and the remainder was in aerospace and defense applications, appliances, automotive electronics, industrial components, and other applications (Jaskula 2010).

Pure beryllium metal is used in aircraft disc brakes, X-ray transmission windows, space vehicle optics and instruments, aircraft and satellite structures, missile parts, nuclear reactor neutron reflectors, nuclear weapons, fuel containers, precision instruments, rocket propellants, navigational systems, heat shields, mirrors, high-speed computers, and audio components. Beryllium alloyed with copper, aluminum, or other metals is used in the electronics, automotive, defense, and aerospace industries. More specifically, beryllium alloys are used in electrical connectors and relays, springs, precision instruments, aircraft engine parts, nonsparking tools, submarine cable housings and pivots, wheels, pinions, automotive electronics, molds for injection-molded plastics, telecommunications devices, computers, home appliances, dental applications, golf clubs, bicycle frames, and many other applications (IPCS 1990, IARC 1993, ATSDR 2002, HSS 2009). Beryllium-copper alloy is used in a wide variety of applications, including electrical connectors and relays, wheels and pinions, nonsparking tools, and switches in automobiles (ATSDR 2002). Beryllium-aluminum alloy has been used in light aircraft construction (Merian 1984). It also may be used in casting alloys, where it refines the grain size, resulting in better surface polishing, reduces melt losses, and improves casting fluidity (IARC 1980, Kaczynski 2002).

Beryllium oxide is the most important high-purity commercial beryllium chemical produced (Kaczynski 2000). It is used in high-technology ceramics, electronic heat sinks, electrical insulators, microwave oven components, gyroscopes, military vehicle armor, rocket nozzles, crucibles, nuclear reactor fuels, thermocouple tubing, laser structural components, substrates for high-density electrical circuits, and automotive ignition systems, and as an additive to glass, ceramics, and plastics (IARC 1993, ATSDR 2002). Beryllium oxide also is used in the preparation of beryllium compounds, as a catalyst for organic reactions, and in high-temperature reactor systems. Beryllium oxide was used in the past in the manufacture of phosphors for fluorescent lamps.

Beryllium chloride is used primarily to manufacture beryllium metal by electrolysis in the laboratory. It also is used as an acid catalyst in organic reactions. Beryllium fluoride and beryllium hydroxide are used commercially in the production of beryllium metal and beryllium alloys, and beryllium fluoride is used in the manufacture of glass and nuclear reactors (Sax and Lewis 1987). Beryllium sulfate is used primarily for the production of beryllium oxide powder for ceramics, and beryllium nitrate is used as a chemical reagent and for stiffening mantles in gas and acetylene lamps (HSDB 2009). The primary use of beryllium sulfate tetrahydrate is as a chemical intermediate in the processing of beryl and bertrandite ores (Sax and Lewis 1987). Beryllium metaphosphate has limited use as a raw material in special ceramic compositions and as a catalyst carrier. Beryllium zinc sulfate was formerly used as an oxygen-dominated phosphor in luminescent materials (IARC 1980, Sax and Lewis 1987).

Production

Beryllium was discovered in 1798, but it did not become commercially important until the 1930s. Although more than 40 beryllium-bearing minerals are known, only two (beryl and bertrandite) currently are commercially important. Beryl ($3\text{BeO}\cdot\text{Al}_2\text{O}_3\cdot 6\text{SiO}_2$), which contains

approximately 11% beryllium oxide (up to 4% beryllium), is the predominant beryllium-containing mineral mined. Beryl is found largely in Brazil and the former Soviet Union. Impurities in beryl include alkali metals, alkaline-earth metals, iron, manganese, and phosphorus. Emeralds (beryl containing chromium), aquamarine (beryl containing iron), and other semiprecious gems are examples of beryl at its purest gem quality (IARC 1993, Jaskula 2009).

U.S. companies have produced beryllium and some beryllium compounds commercially since the 1940s and beryllium oxide since 1958 (IARC 1972). Bertrandite ($4\text{BeO}\cdot 2\text{SiO}_2\cdot \text{H}_2\text{O}$) is the principal beryllium-containing mineral mined in the United States; it contains less than 1% beryllium, but it can be efficiently processed into beryllium hydroxide (IARC 1993). The Topaz-Spor Mountain area of Utah is currently being mined for beryllium; it contains a large reserve of bertrandite, totaling about 15,800 metric tons (35 million pounds) of beryllium (Jaskula 2009). The United States is the world's largest producer of beryllium, accounting for roughly 86% of world production in 2009; total U.S. production was 120 metric tons (265,000 lb), down from 176 metric tons (388,000 lb) in 2008. Other countries producing beryllium (in order of amount produced in 2007) are China, Mozambique, Portugal, Madagascar, and Brazil (Jaskula 2009, 2010).

In 2009, U.S. beryllium consumption, imports, exports, and government stockpile releases were considerably lower than in each of the previous four years (Jaskula 2010). Consumption was 140 metric tons (309,000 lb), down from 220 metric tons (485,000 lb) in 2008; imports for production were 20 metric tons (44,000 lb), down from 70 metric tons (154,000 lb); exports were 30 metric tons (66,000 lb), down from 112 metric tons (247,000 lb); and government stockpile releases were 11 metric tons (24,000 lb), down from 39 metric tons (86,000 lb). In 2009, one U.S. producer of beryllium oxide and one U.S. producer of beryllium sulfate were identified, but no U.S. producers of beryllium nitrate (SRI 2009). U.S. suppliers identified in 2009 included 2 for beryllium, 16 for beryllium oxide, 1 for beryllium hydroxide, 4 for beryllium sulfate, 9 for beryllium sulfate tetrahydrate, 4 for beryllium chloride, 5 for beryllium fluoride, and 2 for beryllium copper alloy (ChemSources 2009).

Natural sources of beryllium and beryllium compounds in the atmosphere (annual amounts) are windblown dust (5 metric tons, or 11,000 lb) and volcanic particles (0.2 metric tons, or 441 lb). Anthropogenic sources include electric utilities (3.5 metric tons, or 7,716 lb), industry (0.6 metric tons, or 1,323 lb), metal mining (0.2 metric tons, or 441 lb), and waste and solvent recovery (0.007 metric tons, or 15 lb) (ATSDR 2002).

Exposure

The primary route of human exposure to beryllium is through inhalation of dusts and fumes (ATSDR 2002). Beryllium may also be ingested in drinking water or food. Beryllium was measured in fruit and fruit juices at concentrations ranging from less than 0.1 $\mu\text{g}/\text{L}$ in a pineapple to 74.9 $\mu\text{g}/\text{L}$ in a papaya. Cigarettes contain beryllium at concentrations of up to 0.0005 μg per cigarette. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 2007 environmental releases totaled 14,185 lb of beryllium from 12 facilities and 862,894 lb of beryllium compounds from 61 facilities (TRI 2009). In measurements at 100 U.S. locations, the average daily beryllium concentration in air was less than 0.0005 $\mu\text{g}/\text{m}^3$. Beryllium was detected at 2,760 of 50,000 U.S. surface-water sites, at an average concentration of 1.9 $\mu\text{g}/\text{L}$, and at 30 of 334 groundwater sites, at an average concentration of 1.7 $\mu\text{g}/\text{L}$. Beryllium occurs naturally in soils at concentrations ranging from less than 1 to 15 mg/kg. The average daily inhalation exposure to beryllium for a U.S. adult was es-

timated at less than 0.0006 μg , and the average daily exposure from food was estimated at 0.12 μg (ATSDR 2002).

The highest levels of human exposure to beryllium are through occupational exposure, which may occur through inhalation of beryllium dust or dermal contact with products containing beryllium. Workers with the highest potential for exposure include beryllium miners, beryllium alloy makers and fabricators, phosphorus manufacturers, ceramics workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers. Occupational exposure may also lead to at-home exposure to beryllium on work garments. In studies in the workplace, air concentrations from personal monitors mounted on clothing increased when the amount of beryllium dust on the fabric increased (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 10,510 workers potentially were exposed to beryllium (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 13,938,000 workers, including 739 women, potentially were exposed to beryllium; 4,305 workers, including 849 women, to beryllium oxide; 1,822 workers, including 230 women, to beryllium sulfate tetrahydrate; and 1,740 workers, including 37 women, to beryllium-copper alloy (NIOSH 1990).

Regulations

Department of Energy (DOE)

DOE has established the Chronic Beryllium Disease Prevention Program to protect workers from excessive beryllium exposure and beryllium disease.

Department of Transportation (DOT)

Numerous beryllium compounds and beryllium compounds not otherwise specified are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Beryllium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Beryllium compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Beryllium and beryllium compounds are listed as a toxic pollutant. Limits have been established for beryllium in biosolids (sewage sludge) when disposed of via incineration.

Beryllium chloride, beryllium fluoride, and beryllium nitrate are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for beryllium; = 1 lb for beryllium chloride, beryllium fluoride, beryllium nitrate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Beryllium and beryllium compounds are listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of beryllium powder = P015.

Beryllium powder and beryllium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.004 mg/L for beryllium.

Food and Drug Administration (FDA)

Maximum permissible level of beryllium in bottled water = 0.004 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Acceptable peak exposure = 0.025 mg/m^3 (30-min maximum duration per 8-h shift) for beryllium and beryllium compounds (as Be).

Ceiling concentration = 0.005 mg/m^3 for beryllium and beryllium compounds (as Be).

Permissible exposure limit (PEL) = 0.002 mg/m^3 for beryllium and beryllium compounds (as Be).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.00005 mg/m³ for beryllium and beryllium compounds (as Be).

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 4 mg/m³ for beryllium and beryllium compounds (as Be).

Beryllium and beryllium compounds are listed as potential occupational carcinogens.

Ceiling recommended exposure limit = 0.0005 mg/m³ for beryllium and beryllium compounds (as Be).

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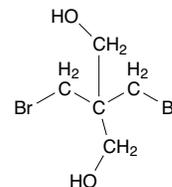
2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)

CAS No. 3296-90-0

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as BBMP



Carcinogenicity

The flame retardant 2,2-bis(bromomethyl)-1,3-propanediol, technical grade, is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2,2-bis(bromomethyl)-1,3-propanediol (BBMP), technical grade, caused tumors at several different tissue sites in rats and mice. In two-year studies, dietary administration of BBMP caused tumors of the oral cavity, esophagus, mammary gland, and thyroid gland in rats of both sexes. In male rats, it also caused mononuclear-cell leukemia and tumors of the skin, subcutaneous tissue, Zymbal gland, forestomach, small and large intestines, mesothelium, urinary bladder, lung, and seminal vesicle. In similar studies with mice, BBMP caused tumors of the Harderian gland and lung in both sexes, the kidney in males, and the subcutaneous tissue in females (NTP 1996, Dunnick *et al.* 1997, IARC 2000). Dietary administration of BBMP for three months, followed by maintenance on a control diet for up to two years, caused tumors in male rats at the same tissue sites as in the two-year study of male rats described above. However, this study found higher incidences of tumors of the oral cavity, forestomach, small and large intestines, lung, Zymbal gland, thyroid gland, and mesothelium than did the two-year study; these tumors were considered to be related to BBMP exposure (NTP 1996, Dunnick *et al.* 1997).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to BBMP (IARC 2000).

Studies on Mechanisms of Carcinogenesis

BBMP caused mutations in *Salmonella typhimurium* strains TA100 and TA1535 only in the presence of mammalian metabolic activation (Zeiger *et al.* 1992). In cultured Chinese hamster ovary cells, BBMP caused chromosomal aberrations only in the presence of mammalian metabolic activation, and it did not cause sister chromatid exchange with or without activation. *In vivo* exposure to BBMP under various conditions induced micronucleus formation in the erythrocytes of mice (NTP 1996). There is no evidence to suggest that mechanisms by which BBMP causes tumors in experimental animals would not also operate in humans.

Properties

BBMP is a brominated alkyl (neopentyl) glycol with an aliphatic neopentyl structure that exists at room temperature as a white solid material with a mild musty odor. It is soluble in water and benzene, very

soluble in acetone, isopropanol, and methanol, and slightly soluble in carbon tetrachloride and xylenes (HSDB 2009). Physical and chemical properties of BBMP are listed in the following table.

Property	Information
Molecular weight	262.0 ^a
Melting point	111°C to 113°C ^a
Log K_{ow}	2.29 ^a
Water solubility	38 g/L at 25°C ^b
Vapor pressure	1.3×10^{-5} mm Hg at 25°C ^b
Dissociation constant (pK_a)	13.57 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

BBMP is used as a flame retardant in unsaturated polyester resins, for molded products, and in the production of rigid polyurethane foam. It is also used as a chemical intermediate in the production of pentaerythritol ethers and other derivatives used as flame retardants (IARC 2000, HSDB 2009).

Production

Annual U.S. production of BBMP was estimated at over 2,300 kg (5,000 lb) in 1977 and 1979 (HSDB 2009) and at 3 million to 4 million pounds in 1983 (NTP 1996). BBMP was listed by the U.S. Environmental Protection Agency as a high-production-volume chemical in 1990, indicating that annual production exceeded 1 million pounds (EPA 2006). In 2009, BBMP was produced by one manufacturer each in the United States, Middle East, and China (SRI 2009) and was available from 14 suppliers, including 7 U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of human exposure to BBMP are inhalation and dermal contact. BBMP may enter the environment as dust and through wastewater (NTP 1996). If released to air, BBMP is expected to exist in both vapor and particulate phases. The half-life of the vapor phase is estimated to be 2 days. If released to water, BBMP is expected to be adsorbed to sediments and suspended solids and not to volatilize from the surface of the water. If released to soil, it is expected to have moderate mobility, based on a soil-water partition coefficient of 420 (HSDB 2009). Occupational exposure to BBMP may occur in industries where it is used as a flame retardant, for example, in production of unsaturated polyester resins, molded products, and rigid polyurethane foam (NTP 1996).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to BBMP were identified.

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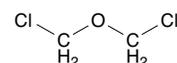
Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

CAS Nos. 542-88-1 and 107-30-2

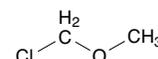
Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as BCME and CMME



Bis(chloromethyl) ether



Chloromethyl methyl ether

Carcinogenicity

Bis(chloromethyl) ether (BCME) and technical-grade chloromethyl methyl ether (CMME) are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous epidemiological studies and case reports from various geographical locations have demonstrated that occupational exposure to BCME or CMME causes lung cancer (predominantly small-cell carcinoma). The risk of lung cancer was shown to increase with increasing exposure duration or cumulative exposure. Among the most heavily exposed workers, the risk of lung cancer was increased at least tenfold, and the time between exposure and diagnosis of disease was shorter. The studies were of workers exposed either to BCME or to CMME; however, because BCME is a contaminant of technical-grade CMME (at levels of 1% to 7%), workers exposed to CMME probably were also exposed to BCME. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in humans (IARC 1974, 1987).

Cancer Studies in Experimental Animals

Exposure to BCME by inhalation caused lung tumors in rats and mice and nasal-cavity tumors in rats. Administration of BCME by subcutaneous injection caused lung tumors in mice of both sexes and connective-tissue tumors (fibroma and/or fibrosarcoma) at the injection site in mice of both sexes and in female rats. Dermal exposure of female mice to BCME caused benign skin tumors (papilloma), most of which progressed to skin cancer (squamous-cell carcinoma). Evaluation of technical-grade CMME is complicated by the presence of BCME as a contaminant. Exposure to technical-grade CMME by inhalation caused a low incidence of respiratory-tract tumors in rats and hamsters, and subcutaneous administration caused tumors at the injection site (sarcoma) in mice. IARC (1987) concluded that there was sufficient evidence for the carcinogenicity of BCME and technical-grade CMME in experimental animals.

Studies on Mechanisms of Carcinogenesis

BCME caused mutations in bacteria. It also caused unscheduled DNA synthesis in cultured human cells but did not cause chromosomal aberrations in bone-marrow cells of rats exposed *in vivo*. CMME caused mutations in bacteria and enhanced virus-induced transformation of mammalian cells. The incidence of chromosomal aberrations was increased slightly in white blood cells from workers exposed to BCME or CMME (IARC 1987).

Properties

BCME is a chloroalkyl ether compound that exists at room temperature as a colorless liquid with a suffocating odor. It is only slightly soluble in water, but it is miscible with ethanol, ethyl ether, and many organic solvents. The compound is unstable in moist air and hydrolyzes rapidly in water (Akron 2009). Physical and chemical properties of BCME are listed in the following table. No physical or chemical properties were identified for technical-grade CMME.

Property	Information (BCME)
Molecular weight	115.0
Specific gravity	1.323 at 15°C/4°C
Melting point	-41.5°C
Boiling point	106°C
Log K_{ow}	1.04
Water solubility	1.020 g/L at 25°C
Vapor pressure	29.4 mm Hg at 25°C
Vapor density relative to air	4

Source: HSDB 2009.

Use

BCME and CMME are used primarily as chemical intermediates and alkylating agents. BCME is used as a laboratory reagent, in the manufacture of plastics, ion-exchange resins, and polymers, and as a monitoring indicator for chloromethyl ether (HSDB 2009). BCME formerly was used for cross-linking of cellulose, for surface treatment of vulcanized rubber to increase adhesion, and in the manufacture of flame-retardant fabrics (ATSDR 1989). CMME is used as an alkylating agent and industrial solvent in the manufacture of dodecylbenzyl chloride, water repellents, ion-exchange resins, and polymers, and as a chloromethylation reagent (HSDB 2009).

Production

BCME and CMME previously were manufactured in the United States, but use of these chemicals had been widely curtailed by 1976 (HSDB 2009). In 1977, U.S. production of BCME was 45,400 kg (100,000 lb), and that of CMME was 4.6 million kilograms (10 million pounds). In 1982, BCME was no longer produced in the United States, and only 2,270 kg (5,000 lb) of CMME was produced. There were three U.S. manufacturers of CMME in 1969, one in 1973, and none in 2009 (IARC 1974a,b, HSDB 2009, SRI 2009). Although BCME is no longer produced commercially in the United States, small quantities may be produced or repackaged as a chemical intermediate or laboratory chemical (ATSDR 1989, HSDB 2009). In 2009, BCME was available from five U.S. suppliers and CMME from nine U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of BCME or CMME were found.

Exposure

The primary routes of potential human exposure to BCME and technical-grade CMME are inhalation and dermal contact. Because BCME is little used in the United States and because it is rapidly degraded in the environment, the probability of human exposure is very low. BCME has not been detected in ambient air or water (ATSDR 1989).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, almost all environmental releases of BCME and CMME have been to the air. Reported annual releases of BCME to air ranged from 255 to 574 lb in the early 1990s, but since 1995, annual releases to air have not exceeded 7 lb, and no releases to air were reported in 1995, 1996, 1998, 2000, or 2009. Releases of CMME to air since 1988 (the earliest year for which reports were available) have fluctuated between 1,000 lb in 1988 and 4,155 lb in 1997. In 2009, one facility reported releases of 3,600 lb of CMME to air (TRI 2009).

The primary route of occupational exposure to BCME or CMME is inhalation of vapors; however, the potential for exposure is low, because these chemicals are no longer produced or sold in large quantities, and most industrial operations involving them take place in closed-process vessels. The most likely means of exposure to BCME is during the production or use of chemicals in which it may occur as a contaminant or may be formed inadvertently. The potential for occupational exposure to BCME or CMME is greatest for chemical plant workers, ion-exchange resin makers, laboratory workers, and polymer makers (ATSDR 1989). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 14 workers (all laboratory workers), including 5 women, potentially were exposed to BCME. No estimate of potential exposure to CMME was reported (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: BCME and CMME are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for BCME and 5,000 lb for CMME.

Clean Water Act

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00010 µg/L for BCME; based on fish or shellfish consumption only = 0.00029 µg/L for BCME.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for BCME and CMME.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: BCME and CMME are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 100 lb for BCME and CMME.

Reportable quantity (RQ) = 10 lb for BCME and CMME.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of BCME = P016 and on the presence of CMME = U046.

BCME and CMME are listed as a hazardous constituents of waste.

Mine Safety and Health Administration

To control airborne exposure, neither BCME nor CMME shall be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

BCME and CMME are listed as a potential occupational carcinogens: Engineering controls, work practices, and personal protective equipment are required.

BCME and CMME are considered highly hazardous chemicals: Threshold quantity (TQ) = 100 lb for BCME; = 500 lb for CMME.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.001 ppm for BCME; = exposure to CMME by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

BCME and CMME are listed as potential occupational carcinogens.

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Bromodichloromethane

CAS No. 75-27-4

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)



Carcinogenicity

Bromodichloromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to bromodichloromethane caused tumors at several different tissue sites in mice and rats. Administration of bromodichloromethane by stomach tube caused benign and malignant kidney tumors (tubular-cell adenoma and adenocarcinoma) in male mice and in rats of both sexes, benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice, and benign and malignant colon tumors (adenomatous polyps and adenocarcinoma) in rats of both sexes (NTP 1987, ATSDR 1989, IARC 1991, 1999).

Since bromodichloromethane was listed in the *Sixth Annual Report on Carcinogens*, additional studies in rats have been identified. Administration of bromodichloromethane in the drinking water increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma or carcinoma) in males (George *et al.* 2002) and caused benign liver tumors (hepatocellular adenoma) in females (Tumasonis *et al.* 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to bromodichloromethane. Several epidemiological studies indicated a possible association between ingestion of chlorinated drinking water (which typically contains bromodichloromethane) and increased risk of cancer in humans, but these studies could not provide information on whether any observed effects were due to

bromodichloromethane or to one or more of the hundreds of other by-products also present in chlorinated water (ATSDR 1989).

Properties

Bromodichloromethane is a trihalomethane that exists as a colorless liquid at room temperature. It is slightly soluble in water and very soluble in ethanol, ethyl ether, benzene, and acetone. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties for bromodichloromethane are listed in the following table.

Property	Information
Molecular weight	163.8
Specific gravity	1.980 at 20°C/4°C
Melting point	-57°C
Boiling point	90°C
Log K_{ow}	2.00
Water solubility	3.96 g/L at 30°C
Vapor pressure	50 mm Hg at 20°C

Source: HSDB 2009.

Use

Bromodichloromethane is used in the synthesis of organic chemicals and as a reagent in laboratory research. It previously was used as a solvent for fats, waxes, and resins, and it has been used to separate minerals and salts, as a flame retardant, and as an ingredient in fire extinguishers (ATSDR 1989).

Production

Bromodichloromethane is not used or produced commercially in the United States. Small quantities have been produced, but production volumes were not found (ATSDR 1989). In 2009, bromodichloromethane was available from 18 suppliers worldwide, including 11 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports were found, but little, if any, trade is expected (ATSDR 1989).

Exposure

Bromodichloromethane is a by-product of water disinfection, and the main route of human exposure is through exposure to chlorine-treated water (IARC 1991). The amount of bromodichloromethane produced during chlorination depends on temperature, pH, the bromide ion concentration of the water, the presence of trihalomethane precursors, and the specific treatment processes (ATSDR 1989). The organic trihalomethane precursors are naturally occurring humic and fulvic acids. The general population is exposed to trihalomethanes through consumption of treated drinking water, beverages, and food products, inhalation of contaminated air, and dermal contact with treated water.

As water-disinfection by-products, trihalomethanes occur at higher concentrations in finished water than in raw waters. It is estimated that bromodichloromethane levels increase by 30% to 100% in water distribution pipes; formation of bromodichloromethane is likely to continue as long as chlorine and organic trihalomethane precursors remain in the water (ATSDR 1989). Since 1998, the concentration of total trihalomethanes in public water systems has been limited to 80 ppb ($\mu\text{g/L}$) (EPA 1998). The highest detected concentration of bromodichloromethane before regulations went into effect was in New Orleans, Louisiana, where its concentration was 11 ppb ($\mu\text{g/L}$) in raw water and 116 ppb in finished water (NRC 1980). In the water supplies of 113 U.S. cities surveyed from 1976 to 1977, the mean bromodichloromethane concentration was 18 ppb (IARC 1991). Bromodichloromethane was detected in 445 of 945 finished water supplies from groundwater sources in a survey conducted from 1981

to 1982, at a median concentration of approximately 1.8 ppb (HSDB 2009), and in 35 of 40 Michigan water supplies at a median concentration of 2.7 ppb (Furlong and D'Itri 1986). Bromodichloromethane was found in 14 of 63 industrial wastewater discharges, at concentrations ranging from less than 10 to 100 ppb (HSDB 2009).

The tap-water uses associated with the greatest bromodichloromethane exposure, based on concentrations of total trihalomethanes in the blood or exhaled breath, were showering, bathing, and hand dishwashing (Ashley *et al.* 2005, Nuckols *et al.* 2005). Ingestion of tap water or hot or cold beverages containing tap water did not increase blood or exhaled breath concentrations. The concentration of bromodichloromethane in the blood increased 3- to 4-fold after showering; for two study sites, the median blood concentrations were 38 and 43 ppt (ng/L) after showering (Nuckols *et al.* 2005), and the median water concentrations of bromodichloromethane were 14 and 12 ppb.

Exposure can also occur from dermal contact with and ingestion of chlorinated swimming-pool water. Individuals who frequent indoor swimming pools and saunas potentially are at higher risk from inhalation exposure (ATSDR 1989). Bromodichloromethane was detected at concentrations of 13 to 34 ppb in chlorinated freshwater pools (Beech *et al.* 1980). Another study examined dermal and inhalation exposure of two college students (one male and one female) to bromodichloromethane during a typical two-hour swimming workout. The results suggested that the main route of exposure was dermal, rather than inhalation, and showed that training was associated with a measurable body burden of bromodichloromethane (Lindstrom *et al.* 1997). Another study found that concentrations of bromodichloromethane in the urine of swimming-pool workers depended on its concentration in the air in the swimming-pool enclosure and increased over the course of a four-hour shift by a factor of 2.5 (Caro and Gallego 2007). At the same pool, concentrations of bromodichloromethane in the urine of swimmers increased by a factor of 3 to 4 after one hour of exercise. Because the workers and swimmers were exposed to the same air concentration of bromodichloromethane, the difference in uptake was attributed to dermal absorption by the swimmers. These results agree with those of a similar study of swimmers that measured bromodichloromethane in alveolar air before and after swimming (Aggazzotti *et al.* 1998).

Although consumers potentially are exposed to bromodichloromethane from contaminated food, resulting from use of chlorinated water to produce these foods, such exposure is not common, and concentrations of bromodichloromethane in food are at or below concentrations in drinking water (HSDB 2009). In the U.S. Food and Drug Administration's Total Diet Study, bromodichloromethane was found in 46 food products, at concentrations ranging from 3 ppb (the limit of quantitation) to 37 ppb (FDA 2003). Bromodichloromethane was detected in cola drinks at concentrations of 2.3 to 3.8 ppb in one study (HSDB 2009); in another study, it was found in non-caramel-colored soft drinks at 0.1 to 0.2 ppb and in cola drinks at 0.9 to 5.9 ppb (Abdel-Rahman 1982).

Bromodichloromethane is not produced on a large commercial scale (HSDB 2009). If contamination occurs from a spill on land, volatilization will occur, which is the predominant environmental removal process, or the compound will leach into groundwater, where significant biodegradation can occur under anaerobic conditions. Bromodichloromethane has a relatively long half-life in air, estimated at 2 to 3 months (ATSDR 1989). Reactions with hydroxyl radicals or singlet oxygen are probably the only identifiable transformation processes in the atmosphere. Long-range global transport is possible. Bromodichloromethane has been detected in rainwater, indicating that washout from the atmosphere is possible; however, it is likely that the compound will volatilize (HSDB 2009). According to the

U.S. Environmental Protection Agency's Toxics Release Inventory, the largest total environmental releases of bromodichloromethane occurred in 1992, when 15,000 lb was released, all as fugitive air emissions. In 2007, one industrial facility released 296 lb of bromodichloromethane to the air (TRI 2009).

The potential for occupational exposure to bromodichloromethane is greatest among workers using it as a reagent for research or to synthesize organic chemicals. Most other uses have been discontinued (ATSDR 1989). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,266 workers, including 502 women, potentially were exposed to bromodichloromethane (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Halomethanes are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.55 µg/L; based on fish or shellfish consumption only = 17 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.080 mg/L for total trihalomethanes (sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform).

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.08 mg/L for total trihalomethanes.

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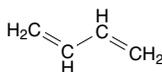
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1,3-Butadiene

CAS No. 106-99-0

Known to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

1,3-Butadiene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. 1,3-Butadiene was first listed in the *Fifth Annual Report on Carcinogens* in 1989 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000.

Cancer Studies in Humans

A number of epidemiological studies have shown an association between occupational exposure to 1,3-butadiene and excess mortality from cancer of the lymphatic and hematopoietic systems. These include (1) a cohort study showing increased risk of lymphosarcoma and reticulosarcoma in workers who manufactured 1,3-butadiene monomer, (2) a study of styrene-butadiene rubber workers in eight plants in the United States and Canada showing increased risk of leukemia among production workers, and (3) a case-control study within the cohort of styrene-butadiene rubber workers showing a large excess of leukemia associated with exposure to 1,3-butadiene and not to styrene (IARC 1992). In addition, an excess of lymphosarcoma and reticulosarcoma was found among 1,3-butadiene production workers in a previously unstudied chemical plant (Ward *et al.* 1996). Excess deaths from leukemia were observed among long-term workers who were hired before 1960 and had worked in the three (of eight studied) styrene-butadiene rubber plants with the highest exposure to butadiene (standardized mortality ratio = 1.8 in comparison with the U.S. population). A second case-control study of styrene-butadiene rubber workers with lymphopietic cancer (with a new set of controls for each case) confirmed the strong association and significant dose-response relationship between 1,3-butadiene exposure score and risk of leukemia (Matanoski *et al.* 1993). Finally, a follow-up study of styrene-butadiene rubber workers in the synthetic rubber industry also found a dose-response relationship between 1,3-butadiene exposure level and the occurrence of leukemia (Delzell *et al.* 1996, 2006, Macaluso *et al.* 1996).

diene exposure level and the occurrence of leukemia (Delzell *et al.* 1996, 2006, Macaluso *et al.* 1996).

Studies on Mechanisms of Carcinogenesis

1,3-Butadiene appears to cause tumors in humans and rodents through its metabolism to DNA-reactive epoxide intermediates, which cause genetic alterations in proto-oncogenes or tumor-suppressor genes (Melnick and Kohn 1995). Mouse, rat, and human liver microsomes have been shown to oxidize 1,3-butadiene to epoxybutene (Csadany *et al.* 1992) and to further oxidize the monoepoxide to diepoxybutane (Seaton *et al.* 1995). These metabolites form *N'*-alkylguanine adducts that have been detected in liver DNA of mice exposed to 1,3-butadiene and in the urine of a worker exposed to 1,3-butadiene. Activated *K-ras* oncogenes and inactivated tumor-suppressor genes observed in 1,3-butadiene-induced tumors in mice are analogous to genetic alterations frequently observed in a wide variety of human cancers. Dose-related increases in *hprt* mutations have been observed in lymphocytes isolated from mice exposed to 1,3-butadiene or its epoxide metabolites and in occupationally exposed workers. The mutational spectra for 1,3-butadiene and its epoxide metabolites at the *hprt* locus in mouse lymphocytes are similar to the mutational spectrum for ethylene oxide, an alkylating agent listed in the Report on Carcinogens as *known to be a human carcinogen*.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 1,3-butadiene from studies in experimental animals. Inhalation exposure to 1,3-butadiene caused benign or malignant tumors at several different tissue sites in rodents, including the hematopoietic system, heart (hemangiosarcoma), lung, forestomach, Harderian gland, preputial gland, liver, mammary gland, ovary, and kidney in mice (NTP 1984, Huff *et al.* 1985, Melnick *et al.* 1990) and the pancreas, testis, thyroid gland, mammary gland, uterus, and Zymbal gland in rats (Owen *et al.* 1987).

Properties

1,3-Butadiene is an olefin which at room temperature is a colorless gas with a mild aromatic or gasoline odor. It is insoluble in water but soluble in ether, ethanol, acetone, and other organic solvents. It polymerizes readily, especially in the presence of oxygen; therefore, it is shipped and stored with an inhibitor to prevent this reaction (Akron 2009). It is also a dangerous fire hazard. Physical and chemical properties of 1,3-butadiene are listed in the following table.

Property	Information
Molecular weight	54.1 ^a
Density	0.6149 g/cm ³ at 25°C ^a
Melting point	-108.966°C ^a
Boiling point	-4.5°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	1.99 ^b
Water solubility	0.735 g/L at 20°C ^a
Vapor pressure	2,110 mm Hg at 25°C ^a
Vapor density relative to air	1.87 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

1,3-Butadiene is used primarily as a monomer to manufacture many different types of polymers and copolymers and as a chemical intermediate to produce a number of important industrial chemicals. More than 75% of the 1,3-butadiene produced goes into synthetic rubber products (CEN 1986). The major uses include production of styrene-butadiene rubber (30% to 35%), polybutadiene rubber (20% to 22%), adiponitrile (12% to 15%), styrene-butadiene latex (10%), neo-

prene rubber (5% to 6%), acrylonitrile-butadiene-styrene resins (5% to 6%), and nitrile rubber (3%), exports (4%), and other uses, including production of specialty polymers (2% to 8%) (IARC 1992, ATSDR 1993). The major end-use products containing styrene-butadiene and polybutadiene are tires. Other products include latex adhesives, seals, hoses, gaskets, various rubber products, nylon carpet backings, paper coatings, paints, pipes, conduits, appliance and electrical equipment components, automotive parts, and luggage. The only major nonpolymer use is in the manufacture of adiponitrile, a nylon intermediate. Butadiene is also used in the manufacture of the fungicides captan and captafol (Morrow 1990, IARC 1992, Kirschner 1996).

Production

1,3-Butadiene is isolated by distillation or extraction from crude butadiene, which is a by-product of ethylene production. Commercial production began in the 1930s (IARC 1992). Between 1980 and 2002, annual U.S. production of rubber-grade 1,3-butadiene ranged from a low of 869,000 metric tons (1.9 billion pounds) in 1982 to a high of 2,009,000 metric tons (4.4 billion pounds) in 2000 (IARC 1992, CEN 1999, 2003). The average annual change was about 2.5% from 1992 to 2002 compared with about 1.2% from 1980 to 1990. 1,3-Butadiene ranked 34th among the top 50 chemical commodities produced in the United States in 1987, falling to 36th by the mid 1990s (Morrow 1990, Kirschner 1996, CEN 1997). In 1990, 30 ethylene plants in the United States produced crude butadiene streams that were processed in 11 extraction plants (Morrow 1990). In 2009, 11 U.S. producers and 12 U.S. suppliers of 1,3-butadiene were identified (ChemSources 2009, SRI 2009). Because U.S. demand for 1,3-butadiene has exceeded the domestic supply in most years, imports have greatly exceeded exports. Annual U.S. imports ranged from 500 million to 900 million pounds from the late 1970s to the mid 1980s and from 1.2 billion to 1.4 billion pounds from 1998 to 2000, decreasing to 200 million pounds in 2002 (ATSDR 1993, USITC 2009). In 2008, imports were 1.7 billion pounds. Annual U.S. exports ranged from 94 million to 145 million pounds from the late 1970s through the mid 1980s, decreasing to 37.6 million pounds in 2000 and 15.2 million pounds in 2002. In 2008, exports were 217.6 million pounds.

Exposure

The primary route of potential exposure to 1,3-butadiene for the general population is inhalation. Some exposure may occur through ingestion of contaminated food or water or dermal contact; however, these routes of exposure are unlikely under most circumstances. 1,3-Butadiene is not a common contaminant of water supplies. Although some food packaging contains residual 1,3-butadiene, the available data indicate that it does not usually migrate to the food. Certain cooking oils, such as rapeseed oil (canola), release 1,3-butadiene when heated (Shields *et al.* 1995).

Most people are exposed to low levels of 1,3-butadiene in the air, because it is released to the environment during its production, use, storage, and disposal and is present in gasoline, automobile exhausts, and cigarette smoke. 1,3-Butadiene is emitted from petroleum refineries and from furnaces at secondary lead smelting facilities handling automotive lead-acid batteries that contain plastic battery separators or that have hard rubber casings (EPA 1996). Incomplete combustion of a variety of fuels forms 1,3-butadiene as a product. 1,3-Butadiene makes up 0.5% to 2% of the total organic gas emissions from most types of combustion (Ligocki *et al.* 1994). It can also be found in motor-vehicle exhaust emissions as a product of incomplete combustion of gasoline and diesel oil and from the thermal breakdown of plastics (ATSDR 1993, EPA 1996). Through modeling of dispersion from a typical freeway source in California, it was estimated that

gasoline-fueled vehicles emit 0.011 g of 1,3-butadiene per mile (Cooper and Reisman 1992). 1,3-Butadiene also is formed naturally as a by-product of forest fires (HSDB 2009). Releases of 1,3-butadiene in sidestream cigarette smoke into the air have been variously estimated at 152 to 400 μg per cigarette (Ligocki *et al.* 1995). Calculations based on 400 μg per cigarette indicate that 1,3-butadiene concentrations in the homes of smokers would be increased by approximately 4 $\mu\text{g}/\text{m}^3$, and concentrations in air at workplaces allowing smoking would be increased by 13 $\mu\text{g}/\text{m}^3$ (Wallace 1991).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, total industrial environmental releases of 1,3-butadiene declined from more than 7.7 million pounds in 1988 to about 1.8 million pounds in 2007, of which over 90% was released to air (TRI 2009). However, a nationwide 1,3-butadiene inventory (including vehicle emissions and emissions from manufacturing and producing facilities) calculated annual butadiene emissions to air to be 102 million kilograms (225 million pounds) in 1990 (Ligocki *et al.* 1994), considerably higher than EPA's estimate of about 5.2 million pounds (2.4 million kilograms) for industrial emissions in the same year.

The median daily concentrations of 1,3-butadiene in U.S. ambient air samples collected from 1970 to 1987 were 0.29 ppb in urban areas (385 samples), 0.32 ppb in suburban areas (196 samples), and 0.1 ppb in rural areas (2 samples). The maximum 24-hour average concentrations of 1,3-butadiene reported for four U.S. cities in 2004 were 0.3 ppb for St. Louis, Missouri, 0.5 ppb for Chicago, Illinois, and Los Angeles, California, and 37.4 ppb for Houston, Texas (Clements *et al.* 2006). However, reported average daily concentrations of 1,3-butadiene in ambient air within a mile of petrochemical facilities have exceeded 100 ppb, and the highest hourly average concentrations have exceeded 900 ppb (ATSDR 1993). Volatilization of 1,3-butadiene from wastewaters of styrene-1,3-butadiene copolymer production at publicly owned treatment works has been calculated to be 21 tons per year (EPA 1996).

Occupational exposure to 1,3-butadiene may occur through inhalation and, to a lesser extent, dermal contact (NTP 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 52,000 workers at 2,201 facilities, including 1,410 women, potentially were exposed to 1,3-butadiene (NIOSH 1990). This estimate does not include workers exposed to butadiene polymers and copolymers and is consistent with an earlier estimate of about 66,000 to 70,000 workers at 3,086 facilities reported in the National Occupational Hazard Survey (conducted from 1972 to 1974) (NIOSH 1976). Health hazard evaluation surveys conducted by the National Institute for Occupational Safety and Health at six facilities found air concentrations of 1,3-butadiene ranging from 0.06 to 39 ppm. Surveys conducted at many monomer, polymer, and end-user plants have reported concentrations ranging from below detection to 374 ppm (827 mg/m^3). In most cases, 8-hour time-weighted-average concentrations were less than 10 ppm ($< 22 \text{ mg}/\text{m}^3$) (IARC 1992, ATSDR 1993). For the monomer industry as a whole, 1,3-butadiene concentrations were greater than 10 ppm ($> 22 \text{ mg}/\text{m}^3$) in 7.1% of the samples, 2 to 10 ppm (4 to 22 mg/m^3) in 12.8%, 1 to 2 ppm (2 to 4 mg/m^3) in 12.3% and less than 1 ppm ($< 2 \text{ mg}/\text{m}^3$) in 67.8%. The Occupational Safety and Health Administration permissible exposure limit is 1 ppm. For the polymer industry as a whole, the corresponding percentages for these four ranges were 3.3%, 7.7%, 3.3%, and 85.8%, respectively. The arithmetic mean exposure for personal full-shift exposures in the polymer plants was 1.14 ppm (2.57 mg/m^3) (Fajen *et al.* 1993).

Regulations

Department of Transportation (DOT)

Butadienes are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.
National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 1,3-butadiene is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Standards have been established for emissions of 1,3-butadiene from reformulated gasoline and motor vehicles.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 ppm.

Short-term exposure limit (STEL) = 5 ppm.

Comprehensive standards for occupational exposure to 1,3-butadiene have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,000 ppm.

Listed as a potential occupational carcinogen.

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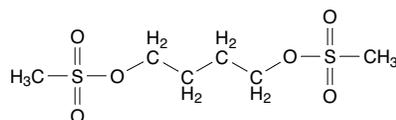
1,4-Butanediol Dimethanesulfonate

CAS No. 55-98-1

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as busulfan; trimethylene methanesulfonate; Busulfex, a registered trademark of Otsuka Pharmaceutical Co., Ltd.; or Myleran, a registered trademark of GlaxoSmithKline, LLC



Carcinogenicity

1,4-Butanediol dimethanesulfonate is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Cases of cytological abnormalities (e.g., giant nuclei, cytomegaly, and dysplasia) and cancer at several different tissue sites, including the breast and female genital organs, were reported among leukemia patients who had been treated with 1,4-butanediol dimethanesulfonate. In a follow-up study of bronchial-cancer patients randomly assigned to treatment with Myleran, cyclophosphamide, or placebo after surgical removal of the tumor, leukemia developed in patients who had received Myleran only, without radiation or other cytotoxic agents; however, the risk of leukemia was not dose-related (IARC 1987).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of 1,4-butanediol dimethanesulfonate in experimental animals is limited. 1,4-Butanediol dimethanesulfonate administered to mice by intraperitoneal injection caused leukemia in one study and T-cell lymphoma in another, but did not increase the incidences of tumors in two other studies. When administered by intravenous injection to female mice, 1,4-butanediol dimethanesulfonate caused thymic lymphoma and ovarian tumors. One study reported that pulmonary lesions (including benign tumors) developed in mice exposed to 1,4-butanediol dimethanesulfonate, but the route of administration was not specified. In rats, 1,4-butanediol dimethanesulfonate did not cause tumors when administered orally. When administered intravenously, it was reported to cause a variety of tumors in male rats, but this study could not be evaluated because of incomplete reporting (IARC 1982, 1987).

Properties

1,4-Butanediol dimethanesulfonate is an alkylsulfonate alkylating agent that exists at room temperature as an off-white granular powder with a slight odor. It has a molecular weight of 246.3 and a melting point of 119°C. It is almost insoluble in water, sparingly soluble in acetone, and slightly soluble in ethanol, and it hydrolyzes in aqueous solution (IARC 1974, Akron, 2009).

Use

1,4-Butanediol dimethanesulfonate is used as a chemotherapeutic agent to treat some forms of leukemia, particularly chronic myelocytic leukemia (IARC 1974, 1982). It also may be used in combination with cyclophosphamide as a conditioning regimen prior to bone marrow transplants for chronic myelogenous leukemia. It is given in tablets or by intravenous injection (FDA 2009, MedlinePlus 2009).

Production

Total annual production of 1,4-butanediol dimethanesulfonate was believed to be less than 500 kg (1,100 lb) in 1974 (IARC 1974). In 2009, no producer of 1,4-butanediol dimethanesulfonate was identified worldwide (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing 1,4-butanediol dimethanesulfonate as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of 1,4-butanediol dimethanesulfonate were found.

Exposure

Patients may be exposed to 1,4-butanediol dimethanesulfonate by ingestion or intravenous administration during chemotherapeutic treatment. 1,4-Butanediol dimethanesulfonate is available as 2-mg oral tablets or in injectable form (6 mg/mL) (FDA 2009). The typical dosage in tablet form is 4 to 8 mg daily (IARC 1974). The recommended intravenous dose prior to a bone-marrow transplant is 0.8 mg/kg of body weight given as a two-hour infusion every six hours for four

days (RxList 2010). Occupational exposure could occur among workers formulating or packaging the tablets or health-care professionals administering the drug. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,764 workers, including 892 women, potentially were exposed to 1,4-butanediol dimethanesulfonate (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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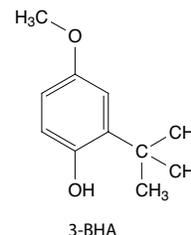
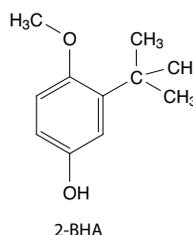
Butylated Hydroxyanisole

CAS No. 25013-16-5

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as BHA or or (1,1-dimethylethyl)-4-methoxyphenol



Carcinogenicity

Butylated hydroxyanisole (BHA) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to BHA caused benign and malignant tumors of the forestomach (papilloma and squamous-cell carcinoma) in rats of both sexes and in male mice and hamsters (IARC 1986, Masui *et al.* 1986). Since BHA was listed in the *Sixth Annual Report on Carcinogens*, an additional study in experimental animals has been identified. Dietary administration of BHA to fish (hermaphroditic *Rivulus marmoratus*) as larvae caused liver cancer (hepatocellular carcinoma) in the adult fish (Park *et al.* 1990).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to BHA. Since BHA was listed in the *Sixth Annual Report on Carcinogens*, one epidemiological study of BHA has been identified. A population-based nested case-control study of stomach cancer in men and women within the Netherlands Cohort Study of dietary intake found no increase in risk at typical levels of dietary intake of BHA (Botterweck *et al.* 2000).

Properties

BHA is an antioxidant which exists at room temperature as a white or slightly yellow, waxy solid with a faint characteristic odor (IARC 1986). BHA in commercial use consists of a mixture of 3-*tert*-butyl-4-hydroxyanisole (3-BHA) and 2-*tert*-butyl-4-hydroxyanisole (2-BHA). BHA is insoluble in water, but is soluble in fats, oils, propylene glycol, petroleum ether, chloroform, and 50% alcohol. Physical and chemical properties of BHA are listed in the following table.

Property	Information
Molecular weight	180.2 ^a
Melting point	48°C to 55°C ^a
Boiling point	264°C to 270°C at 733 mm Hg ^a
Log K_{ow}	3.5 ^b
Water solubility	0.213 g/L at 25°C ^b
Vapor pressure	0.00248 mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

BHA is used primarily as an antioxidant and preservative in food, food packaging, animal feed, and cosmetics, and in rubber and petroleum products (IARC 1986). Food-grade BHA contains over 85% 3-BHA and less than 15% 2-BHA, while cosmetic-grade BHA contains 90% 3-BHA and 8% 2-BHA. Since 1947, BHA has been added to edible fats and fat-containing foods for its antioxidant properties. It is also used in foods cooked or fried in animal oils, because of its high thermal stability and its ability to remain active in baked and fried foods (HSDB 2009). BHA is added to butter, lard, meats, cereals, baked goods, sweets, beer, vegetable oils, potato chips, snack foods, nuts and nut products, dehydrated potatoes, and flavoring agents. It is used in sausage, poultry and meat products, dry mixes for beverages and desserts, glazed fruits, chewing gum, active dry yeast, defoaming agents for beet sugar and yeast, and emulsion stabilizers for shortening (IARC 1986). BHA stabilizes the petroleum wax coatings of food packaging (HSDB 2009). BHA is considered by the U.S. Food and Drug Administration (FDA) to be generally recognized as safe when the antioxidant content does not exceed 0.02% by weight of the food's total fat or oil content.

BHA is one of the primary antioxidants used in feeds, because it retards the oxidation of vitamin A, fats, and vegetable oils. It is an effective stabilizer for essential oils, paraffin, and polyethylenes (HSDB 2009). It is used as an antioxidantizing agent in a biomaterial made from polyurethane and polyethylene oxide used to make mainline catheters (Silverstein *et al.* 1997). BHA is used as a preservative and antioxidant in pharmaceutical preparations and cosmetic formulations containing fats and oils. A 1981 FDA survey found that BHA was used in 3,217 of 21,279 cosmetic formulations; the majority (88%) of the reported concentrations did not exceed 0.1%. In that survey, use of BHA was highest in lipstick formulations (1,256 products), followed by eye-shadow products (410) (IARC 1986). For industrial use, BHA has largely been replaced by *tert*-butylhydroquinone.

Production

In 2009, no producers of BHA were identified worldwide (SRI 2009), but it was available from 46 suppliers, including 18 U.S. suppliers (ChemSources 2009). No recent data on U.S. imports or exports of BHA were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of BHA totaled 10,000 to 500,000 lb in 1986 and 2000, 1 million to 10 million pounds in 1996, and less than 500,000 lb in 2006 (EPA 2004, 2009).

Exposure

Routes of human exposure to BHA are ingestion, inhalation, and dermal contact. In 1975, the estimated average daily intake of BHA in the diet was 4.3 mg (IARC 1986). Estimated annual U.S. use of BHA in food increased from 170,000 kg (374,000 lb) in 1960 to 300,000 kg (660,000 lb) between 1970 and 1982 (IARC 1986). Total reported annual use of BHA in the mid 1970s was 450 metric tons (990,000 lb) (Nicholas *et al.* 1978). The concentration of BHA in six samples of human adipose tissue ranged from 0.01 to 0.03 ppm (Conacher *et al.* 1986). Dermal exposure to BHA occurs from its use as an antioxidant in cosmetic products, especially lipstick and eye shadow (IARC 1986). BHA is also used as an antioxidant for some rubber and petroleum products, and it is a stabilizer for vitamin A (HSDB 2009).

Workers potentially are exposed to BHA in certain industries, including food producers, animal feed producers, livestock producers, cosmetic manufacturers, some petroleum workers, and rubber producers and those who handle the end products, such as tires. Fast-food service personnel who normally cook and serve fried and oily foods potentially are exposed to BHA at high levels; BHA is volatile at 150°C to 170°C (302°F to 338°F) and is readily lost from thermal processes that generate steam (Warner *et al.* 1986). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 89,673 workers, including 44,061 women, potentially were exposed to BHA. Most of these workers were in the Health Services (> 24,000 workers), Food (> 18,000 workers), and Chemical and Allied Products industries (> 13,000 workers) (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

BHA is generally recognized as safe for use in food when the total of antioxidants is not greater than 0.02% of fat or oil content.

BHA may be used as a food additive permitted for direct addition to food for human consumption as prescribed in 21 CFR 172 and 166.

BHA may be used in the manufacture of food packaging materials, with a limit of addition to food of 0.005%.

BHA may be used as an antioxidant in defoaming agents for processed foods, not to exceed 0.1% by weight of defoamer.

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Cadmium and Cadmium Compounds

CAS No. 7440-43-9 (Cadmium)

No separate CAS No. assigned for cadmium compounds as a class

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Cd

Carcinogenicity

Cadmium and cadmium compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. Cadmium and cadmium compounds were first listed as *reasonably anticipated to be human carcinogens* in the *First Annual Report on Carcinogens* in 1980, based on sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be human carcinogens* in the *Ninth Report on Carcinogens* in 2000.

Cancer Studies in Humans

Several epidemiological cohort studies of workers found that exposure to various cadmium compounds increased the risk of death from lung cancer (IARC 1993). Although other factors that could increase the risk of cancer, such as co-exposure to arsenic, were present in several of these studies, it is unlikely that the increased risk

of lung cancer was due entirely to confounding factors. Follow-up analysis of some of these cohorts has not definitively eliminated arsenic exposure as a possibly confounding factor, but has confirmed that cadmium exposure is associated with elevated lung-cancer risk under some industrial circumstances (Sorahan *et al.* 1995, Sorahan and Lancashire 1997). Some early cohort studies found an increased risk of death from prostate cancer among cadmium-exposed workers, but later cohort studies have not confirmed this observation. Additional epidemiological evidence (including case-control studies and geographic-distribution studies) suggests an association between cadmium exposure and cancer of the prostate (Bako *et al.* 1982, Shigematsu *et al.* 1982, Garcia Sanchez *et al.* 1992, van der Gulden *et al.* 1995), kidney (Kolonel 1976, Mandel *et al.* 1995), and urinary-bladder (Siemiatycki *et al.* 1994). The International Agency for Research on Cancer reevaluated the evidence for carcinogenicity of cadmium in 2009 and reaffirmed its earlier conclusion that there was sufficient evidence of cadmium's carcinogenicity in humans. The evidence was classified as sufficient for lung cancer and limited for prostate and kidney cancer (Straif *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

Many studies of cultured mammalian cells have shown that cadmium compounds cause genetic damage, including gene mutations, DNA strand breaks, chromosomal damage, cell transformation, and disrupted DNA repair. Increased frequencies of chromosomal aberrations have been observed in the lymphocytes of workers occupationally exposed to cadmium. The accumulated information, including the carcinogenicity of a wide variety of cadmium compounds, supports the conclusion that ionic cadmium is the genotoxic form of cadmium and its compounds. Therefore, the carcinogenic potential of a given cadmium compound is expected to depend on the degree to which the compound releases ionic cadmium under the conditions of exposure (IARC 1993).

The sensitivity of cells or tissues to cadmium appears to be related, at least in part, to their ability to produce metallothionein, a protective protein that binds heavy metals, including cadmium. Activation of the *MT* gene in response to cadmium exposure results in production of metallothionein, which sequesters cadmium, thus limiting its genotoxic effects. The difference between rats and mice in sensitivity to cadmium as a lung carcinogen appears to be due to differential expression of *MT* in lung tissue following inhalation exposure to cadmium. Other tissues in which cadmium causes cancer in rodents also show minimal basal expression of the *MT* gene or limited activation of *MT* in response to cadmium exposure (Oberdörster *et al.* 1994). There is no evidence to suggest that mechanisms by which cadmium causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Experimental Animals

Cadmium compounds caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Exposure to various cadmium compounds by inhalation or intratracheal instillation caused lung cancer (pulmonary adenocarcinoma) in rats; tumor incidence increased with increasing exposure level. Lung tumors were also observed occasionally in mice exposed to cadmium compounds by inhalation (IARC 1993). When administered orally to rats, cadmium chloride caused dose-related increases in the incidences of leukemia and benign testicular tumors. In several studies with rats and mice, single or multiple injections (subcutaneous, intramuscular, or intraperitoneal) of various soluble and insoluble cadmium compounds caused tumors (sarcoma) at the injection site (IARC 1993, Waalkes and Rehm 1994a).

Subcutaneous injection of cadmium compounds caused tumors at various tissue sites, including prostate tumors in rats, testicular tumors in rats and mice, lymphoma in mice, adrenal-gland tumors in hamsters and mice, and lung and liver tumors in mice (IARC 1993, Waalkes *et al.* 1994, Waalkes and Rehm 1994a,b,c).

Since cadmium and cadmium compounds were listed in the *Ninth Report on Carcinogens*, additional studies in rats have been identified. Subcutaneous administration of cadmium chloride to rats caused pituitary-gland tumors (Waalkes *et al.* 1999a). In rats orally exposed to cadmium chloride, the incidence of kidney tumors increased with increasing exposure level; however, the tumor incidence was not significantly higher at the highest dose than in the unexposed control animals (Waalkes *et al.* 1999b).

Properties

Cadmium is an odorless, silver-white, blue-tinged malleable metal or grayish-white powder. It has an atomic weight of 112.4 and belongs to group IIB of the periodic table. Almost all cadmium compounds have an oxidation state of +2. Cadmium is soluble in dilute nitric acid, ammonium nitrate, and hot sulfuric acid and insoluble in water. It is slowly oxidized in moist air but forms cadmium oxide fumes when heated. Cadmium and cadmium compounds are not combustible but may decompose in fires and release corrosive and toxic fumes. Hot cadmium metal reacts with halogens, phosphorus, selenium, sulfur, and tellurium, and cadmium vapor reacts with oxygen, carbon dioxide, water vapor, sulfur dioxide, sulfur trioxide, and hydrogen chloride. Cadmium is commercially available in purities ranging from 99% to 99.9999%, as powders, foils, ingots, slabs, sticks, and crystals (IARC 1993, Llewellyn 1994, HSDB 2009).

Commercially important cadmium salts include cadmium chloride, cadmium sulfate, and cadmium nitrate. Cadmium chloride occurs as small colorless-to-white rhombohedral or hexagonal crystals. It is soluble in water and acetone, slightly soluble in methanol and ethanol, and insoluble in diethyl ether. Commercial cadmium chloride is a mixture of hydrates similar to the dihydrate form of cadmium chloride. It is available in purities ranging from 95.0% to 99.999%. Cadmium sulfate occurs as colorless to white orthorhombic crystals. It is soluble in water but insoluble in ethanol, acetone, and ammonia, and is available in purities ranging from 98% to 99.999%. Cadmium nitrate occurs as a colorless solid. It is soluble in water, ethanol, acetone, diethyl ether, and ethyl acetate, and very soluble in dilute acids. Cadmium nitrate is available in technical and reagent grades with a purity of 99% or higher (IARC 1993, HSDB 2009).

Other commercially important cadmium compounds include cadmium oxide and cadmium sulfide. Cadmium oxide occurs as a colorless amorphous powder or dark-brown crystals. It is practically insoluble in water, soluble in dilute acids and ammonium salts, and insoluble in alkalis. Commercial-grade cadmium oxide is available in purities ranging from 99% to 99.9999%. Cadmium sulfide occurs as yellow-orange hexagonal or cubic dimorphic semitransparent crystals or as a yellow-brown powder, but may be prepared to range in color from white to deep orange-red. It is practically insoluble in water, insoluble in alkalis, slightly soluble in ammonium hydroxide, and soluble in concentrated or warm dilute mineral acids, with evolution of hydrogen sulfide. Cadmium sulfide is available in purities ranging from 98% to 99.999%; however, many cadmium sulfide products are complex mixtures that contain other metal compounds (IARC 1973, 1993, HSDB 2009).

Use

Cadmium was discovered in 1817 but was not used commercially until the end of the 19th century. The earliest use of cadmium, primar-

ily in the sulfide form, was in paint pigments. Minor amounts were used in dental amalgams in the early 1900s. During World War I, cadmium was used as a substitute for tin. Since World War II, almost all cadmium has been used in batteries, pigments, alloys, electroplating and coating, and stabilizers for plastics (IARC 1993, Llewellyn 1994). However, in the late 20th century, the percentage of cadmium consumed globally in the production of nickel-cadmium (NiCd) batteries increased, while the percentages used in other traditional end uses declined dramatically because of environmental and health concerns (Tolcin 2009b). Electroplating and coating accounted for more than half of cadmium consumption in 1960 but declined to 8% by 2000. Cadmium pigments accounted for 20% to 30% of cadmium consumption between 1970 and 1990 but declined to 12% in 2000. From 1970 to 2000, cadmium's use in stabilizers decreased from 23% to 4%, and its use in alloys from 8% to 1%. In contrast, cadmium's use in batteries grew from 8% in 1970 to 75% in 2000 (IARC 1993, Plachy 2000). In 2009, NiCd battery production was the leading end use of cadmium, followed by pigments, coatings and plating, stabilizers for plastics, nonferrous alloys, and other specialized uses (Tolcin 2009a).

Cadmium chloride is used in electroplating, photocopying, calico printing, dyeing, mirrors, analytical chemistry, vacuum tubes, and lubricants and as a chemical intermediate in production of cadmium-containing stabilizers and pigments (IARC 1993, HSDB 2009). However, its uses are declining. Cadmium chloride was used as a fungicide for golf courses and home lawn turf, but these uses were banned by the U.S. Environmental Protection Agency in the late 1980s (ATSDR 1999). Cadmium sulfate is used in electroplating, fluorescent screens, vacuum tubes, and analytical chemistry; as a chemical intermediate to produce pigments, stabilizers, and other cadmium compounds; as a fungicide or nematocide; and as an electrolyte in Weston cells (portable voltage standards). Cadmium nitrate is used in photographic emulsions, to color glass and porcelain, in nuclear reactors, and to produce cadmium hydroxide for use in alkaline batteries (IARC 1993, HSDB 2009).

Cadmium sulfide is used primarily in pigments for paints, glass, ceramics, plastics, textiles, paper, and fireworks. It is also used in solar cells, fluorescent screens, radiation detectors, smoke detectors, electron-beam-pumped lasers, thin-film transistors and diodes, phosphors, and photomultipliers. Cadmium oxide is used primarily in NiCd batteries, but also as a catalyst and in electroplating, electrical contacts, resistant enamels, heat-resistant plastics, and manufacture of plastics (such as Teflon) and nitrile rubbers. Cadmium oxide has been used as a nematocide and ascaricide in swine (IARC 1993, HSDB 2009).

Production

Cadmium is a rare element, not found in its pure state in nature. It occurs mainly as cadmium sulfide (CdS, or greenockite) in zinc deposits. Cadmium is chiefly recovered as a by-product of zinc concentrates, and its production depends on the demand for zinc (Llewellyn 1994). The United States began commercial production of cadmium in 1907 and was the world's leading producer from 1917 to the late 1960s. U.S. cadmium production peaked in 1969, at 5,740 metric tons (12.7 million pounds) (USGS 2009). Average annual production levels fell to 2,758 metric tons (6 million pounds) for the 1970s, 1,498 metric tons (3.3 million pounds) for the 1980s, 1,437 metric tons (3.2 million pounds) for the 1990s, and 1,196 metric tons (2.6 million pounds) for the 2000s (Tolcin 2009a, USGS 2009). In 2009, the United States and India each produced 700 metric tons (1.54 million pounds) of cadmium, tying them as the ninth-largest producers of cadmium globally (Tolcin 2009a). U.S. production accounted for almost 4% of 2009 world cadmium production. U.S. production of cadmium compounds

was 670 metric tons (1.5 million pounds) in 1999, 460 metric tons (1 million pounds) in 2000, 31 metric tons (68,000 lb) in 2001, and 33 metric tons (73,000 lb) in 2002 (Plachy 2000, 2002). No more recent data on production of cadmium compounds were found.

Eight U.S. companies were identified as major producers of cadmium compounds in the 1990s (ATSDR 1999). Only three U.S. companies were reported to have produced refined cadmium in 2009 (Tolcin 2009a). One company recovered cadmium as a by-product of zinc leaching from roasted sulfide concentrates, and the other two companies thermally recovered cadmium metal from spent NiCd batteries and other cadmium-bearing scrap. In 2010, 15 U.S. suppliers of cadmium metal, 13 suppliers of cadmium metal powder, and numerous suppliers of various cadmium compounds were identified (ChemSources 2010).

U.S. imports of cadmium fell over the late 20th century and early 2000s. Annual cadmium imports averaged 694 metric tons (1.5 million pounds) in the 1960s, 2,088 metric tons (4.6 million pounds) in the 1970s, 2,524 metric tons (5.6 million pounds) in the 1980s, 1,156 metric tons (2.5 million pounds) in the 1990s, and 216 metric tons (476,000 lb) in the 2000s. For 2009, U.S. imports of cadmium were estimated to be 194 metric tons (428,000 pounds). Annual U.S. exports averaged 425 metric tons (937,000 lb) in the 1960s, 188 metric tons (414,000 lb) in the 1970s, 211 metric tons (465,000 lb) in the 1980s, 454 metric tons (1 million pounds) in the 1990s, and 425 metric tons (937,000 lb) in the 2000s. For 2009, U.S. exports were estimated to be 676 metric tons (1.5 million pounds) (Tolcin 2009a, USGS 2009).

Exposure

The general population may be exposed to cadmium through consumption of food and drinking water, inhalation of cadmium-containing particles from ambient air or cigarette smoke, or ingestion of contaminated soil and dust. Tobacco smokers are exposed to an estimated 1.7 µg of cadmium per cigarette. Food is the major source of cadmium exposure for nonsmokers; average cadmium levels in the U.S. food supply range from 2 to 40 ppb. The daily adult intake of cadmium is estimated to be approximately 30 µg, with the largest contribution from grain cereal products, potatoes, and other vegetables. Exposures through drinking water or ambient air typically are very low (ATSDR 1999).

The U.S. Environmental Protection Agency's Toxics Release Inventory (TRI) collects cadmium data in two categories, "cadmium" and "cadmium compounds," and individual facilities may report releases in both categories. From 1988 to 1997, reported releases of cadmium to the environment ranged from about 106,000 to 635,000 lb and releases of cadmium compounds from about 825,000 to 4.1 million pounds. Since 1998 (when the number of industries covered by the TRI was increased), cadmium releases have ranged from a low of about 740,000 lb in 2000 to a high of about 2.8 million pounds in 1998. In 2007, 34 facilities reported releasing about 940,000 lb of cadmium, most of which was released to land on site. Reported releases of cadmium compounds since 1998 have ranged from a low of nearly 8.9 million pounds in 2000 to 3.15 million pounds in 2007, reported by 73 facilities, most of which was released to land on site (TRI 2009).

Workers in a wide variety of occupations potentially are exposed to cadmium and cadmium compounds (IARC 1993). Occupations with the highest potential levels of exposure include smelting zinc and lead ores, welding or remelting cadmium-coated steel, working with solders that contain cadmium, and producing, processing, and handling cadmium powders. The major routes of occupational exposure are inhalation of dust and fumes and incidental ingestion of dust from contaminated hands, cigarettes, or food (ATSDR 1999). The National Occupational Exposure Survey (conducted from 1981

to 1983) estimated that about 250,000 workers potentially were exposed to cadmium and selected inorganic cadmium compounds. These included workers potentially exposed to unknown cadmium compounds (88,968), cadmium sulfide (42,562), cadmium mercury sulfide (19,707), cadmium selenide (17,939), cadmium oxide (15,727), cadmium chloride (4,748), cadmium nitrate (1,878), and cadmium sulfate (1,313) (NIOSH 1990). The Occupational Safety and Health Administration estimated in 1990 that about 512,000 U.S. workers were exposed to cadmium; however, 70% to over 80% were exposed to cadmium at concentrations below the limits set by occupational standards or guidelines (ATSDR 1999).

Regulations

Department of Transportation (DOT)

Cadmium is considered a hazardous material, and cadmium compounds are considered both hazardous materials and marine pollutants, and requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Cadmium compounds are listed as a hazardous air pollutant.

New Source Performance Standards: Regulations have been developed to limit cadmium emissions from new municipal waste combustion units.

Urban Air Toxics Strategy: Cadmium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Cadmium acetate, cadmium bromide, and cadmium chloride are designated as hazardous substances. Limits have been established for cadmium in biosolids (sewage sludge) when used or disposed of via land application or incineration.

Effluent Guidelines: Cadmium and cadmium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for cadmium, cadmium acetate, cadmium bromide, cadmium chloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cadmium and cadmium compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 100 lb for cadmium oxide; = 1,000 lb for cadmium stearate.

Threshold planning quantity (TPQ) = 100 lb for cadmium oxide solids in powder form particle size < 100 µm or solution or molten form; = 1,000 lb for cadmium stearate in powder form particle size < 100 µm or solution or molten form; = 10,000 lb for cadmium oxide and cadmium stearate in all other forms.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for cadmium chloride have been cancelled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 1.0 mg/L for cadmium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of cadmium = F006, K061, K064, K069, K100.

Cadmium and cadmium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L (cadmium).

Food and Drug Administration (FDA)

Maximum permissible level of cadmium in bottled water = 0.005 mg/L.

Various specified color additives may contain cadmium at levels no greater than 15 ppm.

Specified food additives may contain cadmium at maximum levels that range from 0.05 to 0.13 ppm.

Action levels for cadmium in pottery (ceramics) range from 0.25 to 0.5 µg/mL leaching solution.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Ceiling concentration = 0.3 mg/m³ for cadmium fume; = 0.6 mg/m³ for cadmium dust.

Permissible exposure limit (PEL) = 0.005 mg/m³ for cadmium dust and fume.

Comprehensive standards for occupational exposure to cadmium and cadmium compounds have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 mg/m³; = 0.002 mg/m³ for respirable fraction.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 9 mg/m³ for cadmium dust and fume. Cadmium dust and fume are listed as potential occupational carcinogens.

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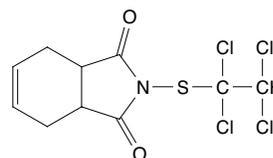
Captafol

CAS No. 2425-06-1

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Difolatan (formerly a registered trademark of Chevron Chemical Company)



Carcinogenicity

Captafol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data on mechanisms of carcinogenesis.

Cancer Studies in Experimental Animals

Oral exposure to captafol caused tumors at several different tissue sites in rats and mice. Long-term feeding studies were conducted with two mouse strains (CD-1 and B6C3F₁) (Ito *et al.* 1984, Quest *et al.* 1993, NTP 2008) and two rat strains (CrI:CD and F344) (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008). In mice of both sexes, tumors were predominantly of the vascular system, gastrointestinal system, and liver; they included (1) cancer of the lymphoid tissue (lymphosarcoma) in CD-1 mice, (2) blood-vessel cancer (hemangiosarcoma) in B6C3F₁ and CD-1 mice, (3) benign tumors of blood vessels of the spleen (splenic hemangioma) in B6C3F₁ mice, (4) benign and malignant tumors of the small intestine in B6C3F₁ mice, and (5) liver cancer (hepatocellular carcinoma) in B6C3F₁ mice. Benign Harderian-gland tumors (adenoma) also were observed in CD-1 males (Ito *et al.* 1984, Quest *et al.* 1993). In rats, captafol caused liver and kidney tumors in several studies and benign mammary-gland tumors (fibroadenoma) in female CrI:CD rats in one study (Nyska *et al.* 1989, Tamano *et al.* 1990, Quest *et al.* 1993). Benign liver tumors (hepatocellular adenoma) were observed in female CrI:CD rats and in F344 rats of both sexes, and a significant dose-related trend was observed for malignant liver tumors (hepatocellular carcinoma) in female F344 rats (Tamano *et al.* 1990, Quest *et al.* 1993, NTP 2008). Captafol caused benign kidney tumors (renal-cell adenoma) in F344 rats of both sexes and malignant kidney tumors (renal-cell carcinoma) in F344 males (Nyska *et al.* 1989, Tamano *et al.* 1990). In CrI:CD rats, the combined incidence of benign and malignant kidney tumors (renal-cell adenoma and carcinoma) was increased in males, and a significant dose-related trend was observed for malignant kidney tumors (renal-cell carcinoma) in both sexes (Quest *et al.* 1993, NTP 2008.)

Captafol was shown to be hepatotoxic and to induce potentially preneoplastic glutathione S-transferase placental form positive (GST-P+) foci in the liver of male F344 rats (NTP 2008) in both the initiation and promotion phases of studies of tumor development. In addition, promotion with captafol increased the incidences of hyperplasia of the forestomach and adenoma of the small intestine (Uwagawa *et al.* 1991), thyroid follicular-cell adenoma (Ito *et al.* 1996), and the expression of a marker of cell proliferation (proliferating-cell nuclear antigen) in the kidney (Kim *et al.* 1997) in F344 rats.

Studies on Mechanisms of Carcinogenesis

In rodents, captafol is absorbed through the gastrointestinal tract and lung and to a lesser extent through the skin; however, the available data indicate that captafol and its metabolites do not accumulate in the tissues of animals and are rapidly eliminated, primarily in the urine. The metabolism and disposition of captafol after oral absorption is anticipated to be similar in experimental animals and humans (NTP 2008). Two metabolic pathways, based primarily on oral absorption, have been proposed; one pathway involves reaction of captafol with cellular thiol-containing molecules such as glutathione and cysteine, and the other involves hydrolysis of the N–S bond. Both pathways are relevant to the mechanism of carcinogenesis, as the reaction of captafol with thiol groups can lead to cytotoxicity, and metabolites derived from the side chain have been shown to be carcinogenic. Tetrahydrophthalimide is a product of both reaction pathways and has been identified in blood, urine, and feces of rats, dogs, and monkeys (Hayes 1982). However, tetrahydrophthalimide has not been tested in carcinogenicity bioassays. Dichloroacetic acid (previously shown to be carcinogenic in mice) was identified as a minor metabolite of captafol in rodents (NTP 2008). Another reported metabolite of captafol is 2-chloro-2-methyl-thioethylene sulfonic acid (which is derived from the side chain) (IPCS 1990). The proposed mechanism for formation of this metabolite is through transient formation of an episulfonium ion, a DNA alkylating agent (IPCS 1990, Williams 1992, Bernard and Gordon 2000).

Short-term *in vitro* and *in vivo* genotoxicity studies support mutagenicity as a mechanism of carcinogenesis. Captafol is an alkylating agent and has produced genotoxic effects in a variety of systems (NTP 2008). It caused mutations in *Salmonella typhimurium* (base-pair mutations) and *Escherichia coli* and in non-mammalian *in vivo* systems (*Aspergillus nidulans* and *Drosophila melanogaster*). In *in vitro* studies with cell lines from rodents and other mammals, captafol caused DNA single-strand breaks, sister chromatid exchange, chromosomal aberrations, micronucleus formation, polyploidy (in one of two studies), mitotic spindle disturbances, and cell transformation. In human cells *in vitro*, it caused DNA single-strand breaks, sister chromatid exchange, micronucleus formation, and chromosomal aberrations. In rodents exposed *in vivo*, captafol caused DNA strand breaks, micronucleus formation (Robbiano *et al.* 2004), and dominant lethal mutations in rats (Collins 1972) but did not cause mutations in the host-mediated assay in rats or dominant lethal mutations in albino mice (Kennedy *et al.* 1975).

In addition to direct genotoxic activity, epigenetic mechanisms, such as cytotoxicity as a result of reduced cellular content of thiol groups (nonprotein and protein), inhibition of enzymes involved in DNA replication (DNA topoisomerases and polymerases), inhibition of DNA and RNA synthesis, and induction of cytochrome P450 mono-oxygenases may also be involved in the pathogenesis of tumor formation (NTP 2008).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure spe-

cifically to captafol. One case-control study (Clary and Ritz 2003) directly addressed captafol exposure. This study was based upon an ecologic (group-level) exposure assessment and included 17 other chlorinated pesticides. A statistically nonsignificant increase in pancreatic cancer was reported among residents who had lived for over 20 years in geographical areas with high captafol use; however, confounding by other cancer risk factors could not be ruled out, and the study was limited by imprecise measures of exposure and diseases.

Properties

Captafol is a broad-spectrum nonsystemic fungicide that is categorized as a phthalimide fungicide based on its tetrahydrophthalimide chemical ring structure (other phthalimide fungicides include captan and folpet). Captafol exists as white, colorless to pale-yellow, or tan (technical grade) crystals or as a crystalline solid or powder, with a slight characteristic pungent odor. It is practically insoluble in water but is soluble or slightly soluble in most organic solvents. Captafol reacts with bases, acids, acid vapors, and strong oxidizers (HSDB 2010). It hydrolyzes slowly in aqueous emulsions or suspensions, but rapidly in acidic and basic aqueous alkaline media (Akron 2010). Captafol will not burn, but when heated to decomposition, it emits toxic fumes, including nitrogen oxides, sulfur oxides, phosgene, and chlorine (IPCS 1993). Physical and chemical properties of captafol are listed in the following table.

Property	Information
Molecular weight	349.1 ^a
Density	1.64 ± 0.1 g/cm ³ at 20°C (calculated from molar volume) ^b
Melting point	160°C to 161°C (decomposes slowly) ^c
Log <i>K</i> _{ow}	3.8 at 25°C ^a
Water solubility	1.4 mg/L at 20°C; 2.24 mg/L at 25°C ^d
Vapor pressure (mm Hg)	8.27 × 10 ⁻⁹ at 20°C ^d
Vapor density relative to air	12 ^e
Dissociation constant (p <i>K</i> _a)	-2.67 ± 0.20 at 25°C ^b

Sources: ^aHSDB 2010, ^bCAS 2008, ^cBCPC 2006, ^dKim *et al.* 1997, ^eAkron 2010.

Use

Captafol is a nonsystemic fungicide used to control fungal diseases of fruits, vegetables, ornamental plants, and grasses and as a seed treatment. It also was used in the timber industry to control wood-rot fungi on logs and wood products (IARC 1991, IPCS 1990). Captafol was produced and used as a fungicide in the United States until 1987, when all registrants of captafol products requested voluntary cancellation of their registrations. Legal use of existing stocks was allowed after 1987; however, in 1999, the U.S. Environmental Protection Agency further restricted its use, and all captafol tolerances were revoked except those for onions, potatoes, and tomatoes. These remaining tolerances were revoked in 2006. Although many countries banned its use, captafol was still used as of the mid 2000s in several countries that exported agricultural products to the United States, including Mexico and Brazil; however, by 2010, no countries were identified that still allowed the use of captafol on food crops.

Production

Captafol is produced by the reaction of tetrahydrophthalimide and 1,1,2,2-tetrachloroethylsulfenyl chloride in the presence of aqueous sodium hydroxide (IARC 1991). It was first registered and produced commercially in the United States in 1961 as Difolatan (IPCS 1993). From 1979 to 1981, annual U.S. production of captafol was estimated to be 3,600 to 4,500 metric tons (8 million to 10 million pounds) (as active ingredient), of which about half was exported (IARC 1991). In 1983, captafol was produced by one U.S. company, whose annual pro-

duction capacity was 12 million pounds (SRI 1984). Production in 1985 was estimated at 6,600 metric tons (14.5 million pounds) (IARC 1991). In 2010, no producers of captafol were identified worldwide (SRI 2010), but Difolatan (a captafol fungicide) was available from ten suppliers, including five in the United States, one in France, one in Hong Kong, two in India, and one in South Africa. In addition, Captafol Pestanal (an analytical standard for captafol) was available from two U.S. suppliers and one Swiss supplier (Chem Sources 2010).

Exposure

In the past, exposure to captafol occurred by ingestion, inhalation, or dermal contact. The potential for exposure of both the general population and agricultural workers would have been greatest from the late 1970s through the mid 1980s, when annual domestic usage was estimated to be at least 4 million pounds. In the past, the general population was potentially exposed to captafol through ingestion of contaminated groundwater or agricultural products sprayed with captafol, through exposure to topsoil, or through its application in nearby agricultural settings. In the United States, captafol was no longer produced after 1987 or used after 2006. It is possible, though highly unlikely, that individuals could be exposed by ingestion of imported fruits or vegetables treated with captafol. The U.S. Food and Drug Administration's Pesticide Residue Monitoring Program and the U.S. Department of Agriculture's Pesticide Data Program detected captafol at low levels in food samples in the 1980s and 1990s, but have not detected it since 1998. No captafol residues were detected in the FDA's Total Diet Study (FDA 1988, 1989, 1993, Yess *et al.* 1993, Gunderson 1995). Between 1993 and 2003, captafol was detected once in animal feed, at a concentration of 0.036 ppm in a barley sample from Maryland in 1999 (FDA 2000).

In air, captafol is expected to exist solely in the particulate phase, based on its vapor pressure; however, some reports suggest that it exists in the vapor phase. In water, captafol is expected to adsorb to sediment and suspended solids. In soil, captafol is expected to have slight mobility, based on its soil organic carbon–water partition coefficient (HSDB 2010). Volatilization from soil is not expected to be an important fate process. Reported values for captafol's half-life soil vary among sources, ranging from less than 3 days to around 11 days (Exttoxnet 1995, HSDB 2010). Captafol has been detected in the vicinity of agricultural uses outside the United States; it was detected in air in Canada (Frank *et al.* 1994), in surface water in Spain (Picó *et al.* 1994, Vioque-Fernandez *et al.* 2007) and Italy (Readman *et al.* 1997), and in soil in India (Venkatramesh and Agnihothrudu 1988). Runoff losses of captafol with natural rainfall were less than 0.1% of the amount applied (Kim *et al.* 1996).

U.S. workers previously were exposed to captafol during its production, formulation, or application to agricultural fields; on reentry to a sprayed field; or when working with treated timber products (IPCS 1993, HSDB 2010). In a study of worker exposure to Difolatan 80 Sprills (80% captafol) in central Florida orange groves, aerosolized captafol concentrations averaged 56 $\mu\text{g}/\text{m}^3$ for mixer-loaders and 34 $\mu\text{g}/\text{m}^3$ for spray applicators. Hourly dermal exposure levels were approximately 1 to 10 $\mu\text{g}/\text{cm}^2$ for the hands, legs, and arms; however, levels of up to 20 $\mu\text{g}/\text{cm}^2$ were seen when direct contact with captafol solution was evident. Whole-body exposures ranged from 15 to 116 mg/h, with a mean of 40 mg/h; the hands accounted for about 40% of total exposure (Popendorf 1988).

Captafol toxicity was reported in exposed workers. Peoples *et al.* (1978) presented 37 brief case reports of exposure during the manufacture and application of captafol that had been reported to the California Department of Food and Agriculture from 1974 through 1976. The reports reflected toxic outcomes of possible captafol ex-

posure that were reported by physicians, including systemic, skin, and eye toxicity. Positive patch tests for captafol or a history of occupationally induced dermatitis were reported in studies of workers who packed captafol (Camarasa 1975), workers exposed to captafol in timber-treatment plants (Stoke 1979), agricultural workers and former agricultural workers (Lisi *et al.* 1986, 1987, Guo *et al.* 1996, Rademaker 1998), flower-shop workers (Thiboutot *et al.* 1990), and laboratory chemists (Brown 1984).

Regulations

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Limitations: Daily discharge maximum = 4.24×10^{-6} kg/kg (kg/metric ton); monthly average discharge maximum = 1.31×10^{-6} kg/kg.

Federal Insecticide, Fungicide, and Rodenticide Act

Classified as Group B, probable human carcinogen based on mammary-gland and liver tumors in female Sprague-Dawley rats, kidney tumors in both male and female rats, and lymphosarcoma and hemangiosarcoma in both male and female CD-1 mice, with Harderian-gland tumors in male mice.

Food and Drug Administration (FDA)

Tolerance levels have been revoked for all foods, thereby making it illegal to import or introduce into commerce any foods with captafol residue.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

Recommended exposure limit (REL) = 0.1 mg/m³.

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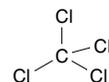
Carbon Tetrachloride

CAS No. 56-23-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as tetrachloromethane



Carcinogenicity

Carbon tetrachloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Carbon tetrachloride caused tumors in several species of experimental animals, at two different tissue sites, and by several different routes of exposure. It caused benign or malignant liver tumors when administered (1) orally in mice and rats of both sexes, in hamsters, and in trout, (2) by subcutaneous injection in male rats, and (3) by inhalation in rats (of unspecified sex) (IARC 1972, 1979). Subcutaneous injection of carbon tetrachloride caused benign and malignant mammary-gland tumors (fibroadenoma and adenocarcinoma) in female rats.

Since carbon tetrachloride was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified. Inhalation exposure to carbon tetrachloride caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) and benign adrenal-gland tumors (pheochromocytoma) in mice of both sexes (Nagano *et al.* 1998, 2007, IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to carbon tetrachloride. Three cases of liver cancer were reported in humans with cirrhosis of the liver who had been exposed to carbon tetrachloride (IARC 1979).

After carbon tetrachloride was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies were identified and reviewed by the International Agency for Research on Cancer. IARC (1999) concluded that there was inadequate evidence in humans for the carcinogenicity of carbon tetrachloride. Statistically nonsignificant increased risks for non-Hodgkin's lymphoma in association with potential exposure to carbon tetrachloride were found among female aircraft-maintenance workers (Blair *et al.* 1998) and in a nested case-control study of rubber workers (Checkoway *et al.* 1984, Wilcosky *et al.* 1984). The latter study also found an increased risk of leukemia. Studies on drycleaning workers were not specific for exposure to carbon tetrachloride (Blair *et al.* 1990, 1993), and IARC considered the population-based case-control studies to be uninformative (IARC 1999).

Since the 1999 IARC review, additional studies have been identified that evaluated the relationship between non-Hodgkin's lymphoma and carbon tetrachloride exposure. Statistically significant risks of non-Hodgkin's lymphoma were reported among individuals with potential exposure to carbon tetrachloride used as a pesticide (McDuffie *et al.* 2001) and among women occupationally exposed to carbon tetrachloride (Wang *et al.* 2009). A small, statistically nonsignificant excess of non-Hodgkin's lymphoma was also found among laboratory workers potentially exposed to carbon tetrachloride and other agents (Kauppinen *et al.* 2003). In an extended follow-up of

the cohort of female aircraft-maintenance workers exposed to carbon tetrachloride, the risk of non-Hodgkin's lymphoma was lower than in the earlier study, although still (nonsignificantly) elevated (Radican *et al.* 2008).

Properties

Carbon tetrachloride is a halomethane that exists at room temperature as a clear, colorless, heavy liquid with a sweetish, aromatic, moderately strong ethereal odor. It is very slightly soluble in water, soluble in ethanol and acetone, and miscible with benzene, chloroform, ether, carbon disulfide, petroleum ether, and oils. It is nonflammable and is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of carbon tetrachloride are listed in the following table.

Property	Information
Molecular weight	153.8
Specific gravity	1.594 at 20°C/4°C
Melting point	-23°C
Boiling point	76.8°C
Log K_{ow}	2.83
Water solubility	793 mg/L at 25°C
Vapor pressure	115 mm Hg at 25°C
Vapor density relative to air	5.32

Source: HSDB 2009.

Use

Carbon tetrachloride is used as a chemical intermediate and as a feedstock in the production of chlorofluorocarbons, such as the Freons dichlorodifluoromethane (F-12) and trichlorofluoromethane (F-11), which are used primarily as refrigerants. It is also used in petroleum refining, in pharmaceutical manufacturing, as an industrial solvent, in the processing of fats, oils, and rubber, and in laboratory applications (IARC 1999, ATSDR 2005, HSDB 2009). It currently is not permitted in products intended for home use (HSDB 2009). Until the mid 1960s, carbon tetrachloride was used as a cleaning fluid both in industry and in the home (in spot removers) and in fire extinguishers (ATSDR 2005). It was also used as a grain fumigant until 1986, when its use for this purpose was cancelled by the U.S. Environmental Protection Agency. Other previous uses include as a rodenticide, as a solvent in some household products, in the formulation of gasoline additives, and in metal recovery and catalyst regeneration (ATSDR 2005, HSDB 2009). In the early 1900s, it was used in human medicine to destroy intestinal parasitic worms, and it was used for a short period as an anesthetic (IARC 1972, ATSDR 2005).

Production

Large-scale U.S. production of carbon tetrachloride began in 1907 (IARC 1979). In 2009, carbon tetrachloride was produced by 26 manufacturers worldwide, including 3 in the United States (SRI 2009), and was available from 69 suppliers, including 19 U.S. suppliers (Chem-Sources 2009). U.S. imports of carbon tetrachloride totaled 110 million kilograms (242 million pounds) in 1989, decreasing to zero 1996; since 1996, only 41 kilograms (90 lb) has been imported. U.S. exports of carbon tetrachloride decreased from 52.7 million kilograms (116 million pounds) in 1989 to 1.7 million kilograms (3.8 million pounds) in 2008 (USITC 2009).

Exposure

The primary routes of potential human exposure to carbon tetrachloride are inhalation, ingestion, and dermal contact. The general population is most likely to be exposed to carbon tetrachloride through air and drinking water. In 1988, EPA's Toxics Release Inventory listed 95

industrial facilities that produced, processed, or otherwise used carbon tetrachloride and reported environmental releases of carbon tetrachloride totaling 3.9 million pounds (TRI 2009). In 1990, 1.7 million pounds was released to air, 36,201 lb to water, and a little over 1,000 lb to soil (ATSDR 2005). In 1999, on-site releases totaled 268,140 lb, and in 2007, 308,633 lb was released by 44 facilities, mostly to underground injection wells or to air (TRI 2009).

Carbon tetrachloride is also formed in the troposphere by solar-induced photochemical reactions of chlorinated alkenes. Because it is readily volatile at ambient temperature and degrades very slowly, it has gradually accumulated in the environment. It is broken down by chemical reactions in air, but so slowly that its estimated atmospheric lifetime is between 30 and 100 years, with 50 years generally regarded as the probable value. In 1988, the average concentration of carbon tetrachloride in air in the United States was reported to be 0.168 ppb, and other studies have observed a steady increase in global atmospheric levels at an annual rate of about 1.3% (IARC 1979). EPA estimated that 8 million people living within 12.5 miles of manufacturing sites were possibly exposed to carbon tetrachloride at an average concentration of 0.5 $\mu\text{g}/\text{m}^3$ and a peak concentration of 1,580 $\mu\text{g}/\text{m}^3$. Point sources of carbon tetrachloride from industry and wind direction are responsible for localized increases in air concentration (ATSDR 2005). A recent study found that during the use of chlorine bleach in cleaning bathrooms and kitchen surfaces, the indoor air concentration of carbon tetrachloride reached 55 $\mu\text{g}/\text{m}^3$; even after 30 minutes, it was measured at 23 $\mu\text{g}/\text{m}^3$ (Odabasi 2008). Based on a typical carbon tetrachloride concentration in ambient air of about 1 $\mu\text{g}/\text{m}^3$ and assuming inhalation of 20 m^3 of air per day by a 70-kg adult and 40% absorption of carbon tetrachloride across the lung, daily inhalation exposure has been estimated at 0.1 $\mu\text{g}/\text{kg}$ of body weight (ATSDR 2005).

Exposure to carbon tetrachloride may also occur by dermal contact with tap water (e.g., during bathing) (ATSDR 2005). Surveys have found that about 99% of all groundwater supplies and 95% of all surface-water supplies contain carbon tetrachloride at a concentration of less than 0.5 $\mu\text{g}/\text{L}$. Exposure to carbon tetrachloride by ingestion may occur through consumption of contaminated drinking water or food. In a study of New Jersey tap water, the maximum monthly estimated concentration of carbon tetrachloride was 7 $\mu\text{g}/\text{L}$, based on measurements by utilities (Bove *et al.* 1995). Based on a typical carbon tetrachloride concentration of 0.5 $\mu\text{g}/\text{L}$ in drinking water, daily consumption of 2 L of water by a 70-kg adult yields an estimated daily intake of about 0.01 $\mu\text{g}/\text{kg}$ of body weight (ATSDR 2005). Exposure from contaminated food is possible, but it is not likely to be of much significance, because levels of carbon tetrachloride in most foods are below the limit of detection. In the U.S. Food and Drug Administration's Total Diet Study, carbon tetrachloride was detected in 41 of 1,331 samples (3%) of 37 food items (FDA 2006). The highest measured concentration was 0.031 mg/kg in one sample of smooth peanut butter, and carbon tetrachloride was detected in two samples of boiled beef frankfurters. Carbon tetrachloride might have been ingested as a contaminant of foods treated before its use as a grain fumigant was banned; in treated stored grain, it was detected at concentrations ranging from 1 to 100 mg/kg (ATSDR 2005).

The greatest risk of occupational exposure to carbon tetrachloride most likely occurred during its use as a fumigant. According to the National Institute for Occupational Safety and Health, the workers most likely to be exposed to carbon tetrachloride are employed at blast furnaces and steel mills, in the air transportation industry, and in motor vehicle and telephone and telegraph equipment manufacturing. It was estimated that 4,500 workers potentially were exposed during production of carbon tetrachloride and 52,000 during

its industrial use. The Occupational Safety and Health Administration estimated that 3.4 million workers potentially were exposed to carbon tetrachloride directly or indirectly. Exposure to carbon tetrachloride may occur in drycleaning establishments, where its concentration in ambient air was found to average between 20 and 70 ppm. Average exposures of 206 and 338 ppm, with excursions to 1,252 and 7,100 ppm, were reported during operation of drycleaning machines. Occupational exposure may also occur during its use in the manufacture of F-11 and F-12. Exposure during fluorocarbon production is most likely for tank-farm and process operators, who may be exposed to emissions from storage-tank vents, from process-equipment leaks or spills, or resulting from transfer of the chemical (NCI 1985). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 77,315 workers, including 12,605 women, potentially were exposed to carbon tetrachloride (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of carbon tetrachloride on ships and barges.

Consumer Product Safety Commission (CPSC)

Carbon tetrachloride and mixtures containing it (with the exception of chemicals containing unavoidable residues of carbon tetrachloride that do not result in atmospheric concentrations of carbon tetrachloride greater than 10 ppm) are banned from consumer products.

Department of Transportation (DOT)

Carbon tetrachloride is considered a hazardous material and marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of carbon tetrachloride is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Carbon tetrachloride is regulated as a Class I substance for stratospheric ozone protection.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.23 µg/L; based on fish or shellfish consumption only = 1.6 µg/L.
 Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for use as a pesticide have been cancelled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of carbon tetrachloride = U211, F001, F024, F025, K016, K019, K020, K021, K073, K116, K150, K151, K157.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.
 All medical devices containing or manufactured with carbon tetrachloride must contain a warning statement that the compound may destroy ozone in the atmosphere.

Mine Safety and Health Administration

Carbon tetrachloride use is banned in metal and non-metal surface and underground mines.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
 Permissible exposure limit (PEL) = 10 ppm.
 Ceiling concentration = 25 ppm.

Acceptable peak exposure = 200 ppm (maximum duration = 5 min in any 4 h).
 Carbon tetrachloride can not be used as a fire extinguishing agent where employees may be exposed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 ppm.
 Threshold limit value – short-term exposure limit (TLV-STEL) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Short-term exposure limit (STEL) = 2 ppm (12.6 mg/m³) (60-min exposure).
 Immediately dangerous to life and health (IDLH) limit = 200 ppm.
 Listed as a potential occupational carcinogen.

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Ceramic Fibers (Respirable Size)

CAS No.: none assigned

Reasonably anticipated to be human carcinogens

First listed in the *Seventh Annual Report on Carcinogens* (1994)

Also known as refractory ceramic fibers

Carcinogenicity

Ceramic fibers of respirable size are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to ceramic fibers by inhalation caused benign or malignant lung tumors in rats of unspecified sex (IARC 1988). Since ceramic fibers (respirable size) were listed in the *Seventh Annual Report on Carcinogens*, additional studies in rodents have been identified. The induction of benign and malignant lung tumors following inhalation of ceramic fibers was confirmed in rats (adenoma, carcinoma, and histiocytoma) and also observed in hamsters (adenoma and carcinoma). In addition, mesothelioma of the pleural membrane was observed following exposure by inhalation in rats and male hamsters (Hesterberg *et al.* 1993, Rossiter and Chase 1995, McConnell *et al.* 1996, IARC 2002) and intrapleural injection in rats, and fibrosarcoma or mesothelioma of the peritoneum was observed following exposure by inhalation in rats and intraperitoneal injection in female hamsters and rats of both sexes (IARC 2002).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to respirable ceramic fibers. Since ceramic fibers (respirable size) were listed in the *Seventh Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer (IARC 2002) concluded that the data available did not permit evaluation of the carcinogenicity of refractory ceramic fibers in humans, because the studies (Chiazze *et al.* 1997, Walker *et al.* 2002) were either preliminary or limited by small numbers. Since the IARC evaluation, a study of two refractory ceramic fiber manufacturing plants reported a significant threefold excess of urinary cancer (mainly urinary-bladder cancer) based on five deaths, but no excesses of lung cancer or mesothelioma (LeMasters *et al.* 2003).

Properties

Ceramic fibers comprise a wide range of amorphous or crystalline synthetic mineral fibers characterized by their refractory properties (i.e., stability at high temperatures) (IARC 1988). They typically are made of alumina, silica, and other metal oxides or, less commonly, of nonoxide materials such as silicon carbide. Most ceramic fibers are composed of alumina and silica in an approximate 50/50 mixture. By definition, monoxide ceramics, such as alumina and zirconia, are composed of at least 80% of one oxide; they generally contain 90% or more of the base oxide, and specialty products may contain virtually 100%. Nonoxide specialty ceramic fibers, such as silicon carbide, silicon nitride, and boron nitride, also have been produced. Because

there are several types of ceramic fibers, such fibers exhibit a range of chemical and physical properties. Most ceramic fibers are white to cream in color and tend to be polycrystallines or polycrystalline metal oxides.

Use

Ceramic fibers are used as insulation materials, because of their ability to withstand high temperatures, and are used primarily for lining furnaces and kilns (IARC 1988, 2002). The products are in the form of blankets, boards, felts, bulk fibers, vacuum-formed or cast shapes, paper, and textiles. Their light weight, thermal-shock resistance, and strength make them useful in a number of industries. High-temperature resistant ceramic blankets and boards are used in shipbuilding as insulation to prevent the spread of fires and for general heat containment. Blankets, rigid boards, and semirigid boards can be applied to the compartment walls and ceilings of ships for this purpose. Ceramic blankets are used as insulation for catalytic converters in the automobile industry and in aircraft and space-vehicle engines. In the metal industry, ceramic blankets are used as insulation on the interior of furnaces. Boards are used in combination with blankets for insulation of furnaces designed to produce temperatures up to about 1,400°C. Ceramic boards are also used as furnace and kiln backup insulation, thermal covering for stationary steam generators, linings for ladles designed to carry molten metal, and cover insulation for magnesium cells and high-temperature reactors in the chemical-process industry. Ceramic textile products, such as yarns and fabrics, are used extensively in such end products as heat-resistant clothing, flame curtains for furnace openings, thermocoupling and electrical insulation, gasket and wrapping insulation, coverings for induction-heating furnace coils, cable and wire insulation for braided sleeving, infrared radiation diffusers, insulation for fuel lines, and high-pressure portable flange covers. Ceramic fibers coated with Teflon are used as sewing threads for manufacturing high-temperature insulation shapes for aircraft and space vehicles. The spaces between the rigid tiles on space shuttles are packed with this fiber in tape form. Ceramic fibers are also used for space-shuttle tiles and other heat shields in the aerospace industry (NIOSH 2006).

Ceramic fibers have consumer applications in the automotive industry, commercial and domestic appliances, commercial fire protection, and hobby furnaces. In the automotive industry, papers and felts containing ceramic fibers are used in catalytic converters, heat shields, air bags, brake pads, clutch facings, and shoulder-belt controls. Commercial and domestic appliances using ceramic-fiber insulation include pizza-oven and deep-fryer heat shields, toasters, self-cleaning ovens, wood stoves, home-heating furnaces, gas hot-water heaters, and simulated fireplace logs. In commercial fire protection, ceramic fibers are used in grease-duct insulation and penetration and expansion-joint seals. They are also used in hobby furnaces, such as ceramic pottery and glass-enameling kilns and blacksmith forges (Venturin *et al.* 1997, NIOSH 2006).

Production

Ceramic fibers are produced by blowing and spinning, colloidal evaporation, continuous filamentation, and, to a lesser extent, whisker-making technologies (vapor-phase deposition used mainly for special applications). Although production of ceramic fibers began in the 1940s, they were not used commercially until the early 1970s (IARC 1988). Worldwide production of ceramic fibers in the early to mid 1980s was estimated at 154 million to 176 million pounds, with U.S. production accounting for about half. U.S. production was estimated at 85.7 million pounds in 1990 and 107.7 million pounds in 1997 (NIOSH 2006). In 2004, U.S. production by four major producers

had fallen to 80 million pounds, accounting for 1% to 2% of world-wide production.

Exposure

The routes of potential human exposure to ceramic fibers include ingestion and dermal contact; however, the primary route of exposure is inhalation during their manufacture, processing, and end use. Manufactured mineral-fiber products release airborne respirable fibers during their production and use. The upper-diameter limit for respirable fibers is considered to be 3 or 3.5 μm . In three refractory ceramic fiber manufacturing facilities, about 90% of airborne fibers were determined to be respirable ($< 3 \mu\text{m}$ in diameter), and about 95% were less than 50 μm long (NIOSH 2006). It was estimated that 31,500 workers potentially were exposed to refractory ceramic fibers during their manufacture, processing, and end use, of whom only about 800 were involved in the manufacturing process (Rice *et al.* 2005).

In the U.S. manufacturing sector, the workplace time-weighted average (TWA) air concentration of refractory ceramic fibers was 10 fibers/cm³ in the 1950s, decreasing to 0.05 to 2.6 fibers/cm³ by the 1970s. Concentrations in the 1980s ranged from the level of detection to 0.66 fibers/cm³. Average TWA exposures were 0.31 fibers/cm³ between 1993 and 1998 and 0.2 fibers/cm³ between 2002 and 2006. End users were exposed to refractory ceramic fibers at higher concentrations than were manufacturing workers; average air concentrations for end users were 0.56 fibers/cm³ between 1993 and 1998 and 0.1 fibers/cm³ between 2001 and 2005. TWA air concentrations were highest for workers engaged in removal of refractory ceramic fibers, averaging 1.92 fibers/cm³ between 1993 and 1998, but decreasing to 1.27 fibers/cm³ between 2001 and 2005. Starting in 2002, respirator use was required during the removal process; between 2002 and 2006, the average TWA concentration adjusted for respirator protection was 0.28 fibers/cm³, much lower than the measured ambient concentration. The respirator-use rate was low for job categories with lower measured ambient concentrations of refractory ceramic fibers and higher in workplaces with high ambient concentrations (NIOSH 2006, Maxim *et al.* 2008). A study conducted among Ontario construction workers found that 40% of the measured ambient exposure concentrations exceeded the American Conference of Governmental Industrial Hygienists threshold limit value—TWA recommended concentration of 0.2 fibers/cm³, indicating the need for additional controls, such as adequate ventilation and the use of respirators (Verma *et al.* 2004).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Fine mineral fibers are listed as a hazardous air pollutant.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 15 mg/m³ total fibers; = 5 mg/m³ respirable fibers (based on the standard for particulates not otherwise regulated).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 respirable fibers/cm³ for refractory ceramic fibers.

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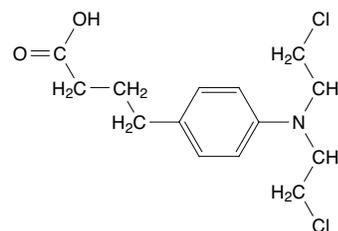
Chlorambucil

CAS No. 305-03-3

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 4-[*p*-[bis(2-chloroethyl)amino]phenyl]butyric acid



Carcinogenicity

Chlorambucil is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have linked treatment with chlorambucil, either alone or in combination with other therapies, with development of cancer, primarily acute nonlymphocytic leukemia, in patients who were treated for other types of cancer or other (nonmalignant) diseases. In addition, a few small epidemiological studies found excesses of cancer in patients treated with chlorambucil. In a randomized clinical trial with 431 polycythemia vera patients, the incidence of acute nonlymphocytic leukemia was 13-fold higher in patients treated with chlorambucil plus phlebotomy than in patients treated with phlebotomy alone, and the risk of leukemia increased with increasing dose and duration of treatment (IARC 1981, 1987).

Cancer Studies in Experimental Animals

Chlorambucil administered by intraperitoneal injection caused tumors of the hematopoietic system in mice of both sexes (lympho-

sarcoma) and in male rats (lymphosarcoma, myelogenous leukemia, and reticulum-cell sarcoma). In mice, it also caused lung tumors in both sexes and ovarian tumors in females. In an initiation-promotion study, chlorambucil acted as a skin-tumor initiator when croton oil was used as the promoter (IARC 1981, 1987). The International Agency for Research on Cancer (IARC 1987) concluded that there was sufficient evidence for the carcinogenicity of chlorambucil in experimental animals.

Properties

Chlorambucil is a nitrogen mustard that acts as a bifunctional alkylating agent and is used as a pharmaceutical agent (IARC 1987). It exists at room temperature as an off-white granular powder with a slight odor. It is soluble in ethanol, chloroform, ethyl acetate, benzene, and ether, and readily soluble in acid or alkaline solutions. In water, the free acid is insoluble, but the sodium salt is soluble. Chlorambucil is sensitive to oxidation and moisture (IARC 1981). Physical and chemical properties of chlorambucil are listed in the following table.

Property	Information
Molecular weight	304.2 ^a
Melting point	64°C to 66°C ^a
Log K_{ow}	1.47 at pH 7.4 ^a
Water solubility	12.4 g/L at 25°C ^b
Vapor pressure	5.7×10^{-8} mm Hg at 25°C ^a
Dissociation constant (pK_a)	5.75 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Chlorambucil is used primarily as an antineoplastic agent to treat cancer of the blood and lymphatic system, such as Hodgkin's and non-Hodgkin's lymphoma, chronic lymphocytic leukemia, and primary (Waldenström's) macroglobulinemia. It is also used as a chemotherapeutic agent for Kaposi's disease and cancer of the breast, lung, cervix, ovary, and testis. Chlorambucil is an immunosuppressive agent that has been used to treat rheumatoid arthritis, systemic lupus erythematosus, acute and chronic glomerular nephritis, nephrotic syndrome, psoriasis, Wegener's granulomatosis, chronic active hepatitis, and cold agglutinin disease (IARC 1981). It is also used in veterinary medicine to treat cancer and immune-mediated diseases, including lymphocytic leukemia, multiple myeloma, ovarian cancer, lymphoma, polycythemia rubra vera, pemphigus diseases, eosinophilic granuloma complex, inflammatory bowel disease, feline infectious peritonitis, immune-mediated hemolytic anemia, and immune-mediated platelet destruction (Brooks 2009).

Production

All of the chlorambucil used in the United States is imported from the United Kingdom (HSDB 2009). However, the drug has been formulated in the United States since 1957. Annual U.S. sales of chlorambucil in the mid 1970s were estimated at less than 20 kg (44 lb) (IARC 1975). In 2009, chlorambucil was available from six U.S. suppliers (ChemSources 2009), and one product approved by the U.S. Food and Drug Administration contained chlorambucil as the active ingredient (FDA 2009). Annual U.S. imports of chlorambucil were 32 to 34 kg (71 to 75 lb) in the early 1970s, increasing slightly to 48 kg (106 lb) in 1978 (IARC 1981, HSDB 2009).

Exposure

The primary routes of potential human exposure to chlorambucil are ingestion, inhalation, and dermal contact. Continuous and intermittent oral-treatment schedules are employed for patients treated with chlorambucil. Chlorambucil is available in 2-mg tablets. The initial

daily dose is 0.1 to 0.2 mg/kg of body weight (for a total daily dose of 4 to 10 mg) for 3 to 6 weeks. If clinical improvement or bone-marrow toxicity occurs, the dose is reduced. A daily maintenance dose of 2 mg may be required (IARC 1981, FDA 2009). Occupational exposure to chlorambucil may occur through dermal contact or inhalation of dust during formulation, packaging, and administration of the drug product. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,719 workers, including 2,018 women, potentially were exposed to chlorambucil (NIOSH 1990). No more recent estimates of exposure were found.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of chlorambucil = U035.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Chlorambucil is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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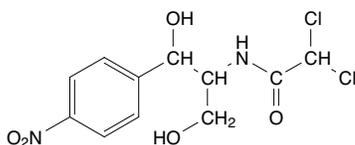
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Chloramphenicol

CAS No. 56-75-7

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Chloramphenicol is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia, and three case reports have documented the occurrence of leukemia after chloramphenicol therapy in the absence of intervening aplastic anemia (IARC 1990). A case-control study in China found an increased risk of leukemia in children who had been treated with chloramphenicol; the risk increased significantly with increasing number of days the drug was taken (Shu *et al.* 1987, 1988). Two case-control studies found large but statistically nonsignificant increases in the risk of aplastic anemia associated with use of chloramphenicol in the six months before the onset of aplastic anemia (Issaragrisil *et al.* 1997, Laporte *et al.* 1998). However, two other case-control studies found no association between the use of chloramphenicol and the risk of leukemia in adults, suggesting that children may be a particularly susceptible subgroup (Zheng *et al.* 1993, Doody *et al.* 1996). One case-control study found an association between chloramphenicol use and increased risk of soft-tissue sarcoma (Zahm *et al.* 1989). Considered together, the many case reports implicating chloramphenicol as a cause of aplastic anemia, the evidence of a link between aplastic anemia and leukemia, and the increased risk of leukemia found in some case-control studies support the conclusion that chloramphenicol exposure is associated with an increased risk of cancer in humans.

Studies on Mechanisms of Carcinogenesis

Chloramphenicol inhibits protein synthesis in the mitochondria of mammalian cells (by binding to ribosomes), which accounts for the sensitivity of proliferating tissues, such as those that promote the formation of blood cells, to its toxicity. Anemia, including aplastic anemia, is a recognized hazard associated with chloramphenicol treatment in humans. In genotoxicity studies, chloramphenicol gave mainly negative results in bacterial systems and mixed results in mammalian systems. The most consistently positive results were observed for cytogenetic effects in mammalian cells, including DNA single-strand breaks and increased frequencies of sister chromatid exchange and chromosomal aberrations. Overall, chloramphenicol appears to be genotoxic (NTP 2000). Several studies have suggested that dehydrochloramphenicol, a chloramphenicol metabolite produced by intestinal bacteria, may be responsible for DNA damage and carcinogenicity (Isildar *et al.* 1988a,b, Jimenez *et al.* 1990, Kitamura *et al.* 1997). This metabolite can undergo nitroreduction in the bone marrow and has been shown to cause DNA single-strand breaks in bone-marrow cells. Mitochondrial abnormalities caused by chloramphenicol are similar to those observed in preleukemia, sug-

gesting that mitochondrial DNA is involved in the pathogenesis of secondary leukemia.

Cancer Studies in Experimental Animals

No adequate studies of the carcinogenicity of chloramphenicol in experimental animals were identified. In male mice given chloramphenicol by intraperitoneal injection in combination with busulfan (the known human carcinogen 1,4-butanediol dimethanesulfonate), the incidence of lymphoma was significantly higher than in mice receiving either busulfan or chloramphenicol alone (Robin *et al.* 1981).

Properties

Chloramphenicol is a naturally occurring antibiotic derivative of dichloroacetic acid that is a white to grayish or yellowish-white fine crystalline powder at room temperature. It is soluble in water and very soluble in methanol, ethanol, butanol, ethyl acetate, chloroform, and acetone. It is fairly soluble in ether, but insoluble in benzene, petroleum ether, and vegetable oils (IARC 1990, HSDB 2009). It is stable under normal shipping and handling conditions (Akron 2009). The biologically active form of chloramphenicol is levorotatory (Chambers 2001). Physical and chemical properties of chloramphenicol are listed in the following table.

Property	Information
Molecular weight	323.1
Melting point	150°C to 152°C
Log K_{ow}	1.14
Water solubility	25 g/L at 25°C
Vapor pressure	1.7×10^{-12} mm Hg at 25°C

Source: HSDB 2009.

Use

Chloramphenicol is an antimicrobial agent with restricted use, because it causes blood abnormalities. It is used to combat serious infections for which other antibiotics are either ineffective or contraindicated. It can be used against gram-positive cocci and bacilli and gram-negative aerobic and anaerobic bacteria (Burnham *et al.* 2000). Chloramphenicol has been used since the 1950s to combat a wide range of microbial infections, including typhoid fever, meningitis, and certain infections of the central nervous system (IARC 1990). It currently is used in eye ointments and drops to treat superficial ocular infections involving the conjunctiva or cornea, in topical ointments or drops to treat the external ear or skin, in tablets for oral administration, and in intravenous suspensions to treat internal infections (FDA 2009, MedlinePlus 2009). Chloramphenicol has also been used in veterinary medicine as a highly effective and well-tolerated broad-spectrum antibiotic. Because of its tendency to cause blood abnormalities in humans, the U.S. Food and Drug Administration in 1997 banned its use in food-producing animals. Chloramphenicol continues to be used to treat both systemic and local infections in cats, dogs, and horses (FDA 1997, Brooks 2008).

Production

Chloramphenicol is produced naturally by the bacterium *Streptomyces venezuelae*. It may be produced by chemical synthesis followed by a step to isolate stereoisomers. A fermentation process also has been described that does not require separation of stereoisomers (IARC 1990). Chloramphenicol was first produced in the United States in 1948 (IARC 1990). Annual U.S. production was estimated to exceed 908 kg (2,000 lb) in 1977 and 1979 (HSDB 2009). In 2009, chloramphenicol was produced by 16 manufacturers worldwide, including 11 in India, 1 in China, 2 in East Asia, and 2 in Europe (SRI 2009). U.S.

imports of chloramphenicol were estimated at 8,150 kg (17,970 lb) in 1977 and 8,200 kg (18,080 lb) in 1979 (HSDB 2009). Since 1989, annual imports of chloramphenicol and its derivatives have remained at or below 16,000 kg (35,000 lb), averaging 8,000 kg (18,000 lb) from 1989 to 2004. Over the same period, annual U.S. exports of chloramphenicol were less than 53,000 kg (117,000 lb) except in 1993, when 1.9 million kilograms (4 million pounds) were exported. No exports were reported for 1998 or 2000 (USITC 2009). In 2002, less than 10,000 lb of chloramphenicol (U.S. production plus imports) was reported under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule; no inventory update reports for chloramphenicol were filed before 2002 (EPA 2004).

Exposure

The primary routes of human exposure to chloramphenicol are oral and dermal, through its use as a drug. Exposure also may occur through inhalation, dermal contact, ingestion, or contact with contaminated water or soil (HSDB 2009). For adults, a typical dosage of chloramphenicol is 50 to 100 mg/kg of body weight per day, divided into four oral or intravenous doses (MedlinePlus 2009). Chloramphenicol also is used in ophthalmic ointments, solutions, and drops. It usually is taken for two to five days or until the infection is diminished. For many infections, continued treatment with chloramphenicol after the infection has resolved is suggested, for periods ranging from 48 hours for eye infections to 8 to 10 days for typhoid fever. No information was found on the number of prescriptions currently written for chloramphenicol in the United States. Children, especially newborns and young infants, metabolize chloramphenicol much more slowly than do adults. Pediatric doses must be lower so as to avoid gray-baby syndrome; this syndrome is characterized by cardiovascular collapse in infants, apparently caused by accumulation of active, unconjugated chloramphenicol in the serum, resulting from low inactivation through glucuronide conjugation in the liver (Chambers 2001). Initial dosages are 25 mg/kg of body weight every 24 hours for infants under one week old, 25 mg/kg every 12 hours for infants aged one to four weeks, and 50 mg/kg every 6 hours for children weighing less than about 25 kg (55 lb) (Sills and Boenning 1999).

Chloramphenicol can be detected in blood serum, plasma, cerebrospinal fluid, and urine. It is rapidly absorbed from the gastrointestinal tract and is distributed extensively through the human body, regardless of administration route. It has been found in the heart, lung, kidney, liver, spleen, pleural fluid, seminal fluid, ascitic fluid, and saliva. Upon metabolism, chloramphenicol yields *D*-*threo*-2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and chloramphenicol- β -*D*-glucuronide (IARC 1990). Following degradation of chloramphenicol by intestinal bacteria via amidolysis, 18 metabolites were observed, the major ones being 2-amino-1-(*p*-nitrophenyl)-1,3-propanediol and its *p*-aminophenyl reduction by-product (HSDB 2009). Approximately 90% of chloramphenicol is excreted in urine, mostly as metabolites, including conjugated derivatives; only 15% is excreted as the parent compound (IARC 1990). The half-life of chloramphenicol in adult humans ranges from 1.6 to 4.6 hours. Peak levels appear two to three hours after oral administration of chloramphenicol. In adults given eight 1-g doses, once every six hours, the average peak serum level was 11.2 μ g/mL one hour after the first dose and 18.4 μ g/mL after the fifth dose. Mean serum levels ranged from 8 to 14 μ g/mL over the 48-hour period (Burnham *et al.* 2000). In infants, chloramphenicol's half-life is much longer, ranging from 10 to more than 48 hours in infants aged one to eight days and from 5 to 16 hours in infants aged eleven days to eight weeks (IARC 1990).

Chloramphenicol is released to the environment and may be found in various waste streams as a result of its use as a medicinal and re-

search antimicrobial agent. Chloramphenicol may also be isolated from *S. venezuelae* of the soil (HSDB 2009). If released to air, chloramphenicol will exist primarily as an aerosol and will be removed mainly through dry deposition. Chloramphenicol in the atmosphere reacts with photochemically produced hydroxyl radicals, with a half-life of 12 hours. If released to water, chloramphenicol will be essentially nonvolatile. Adsorption to sediment and bioconcentration in aquatic organisms are not expected to be important processes. If released to soil, chloramphenicol is expected to have high mobility. It is not expected to evaporate from either dry or wet soils. Various studies indicate that chloramphenicol may biodegrade in soil and water. It was found to degrade in adapted activated waste sludge (HSDB 2009).

Occupational exposure during the manufacture of chloramphenicol may occur through inhalation, dermal contact, or ingestion (HSDB 2009). Medical and veterinary personnel who administer drugs containing chloramphenicol also may be exposed (Burnham *et al.* 2000, Brooks 2008).

Regulations

Food and Drug Administration (FDA)

Chloramphenicol is a prescription drug subject to specific labeling requirements.

Extra-label use of chloramphenicol in food-producing animals is prohibited.

Chloramphenicol in ophthalmic and topical dosage form and in tablet form must not be used in animals producing meat, eggs, or milk.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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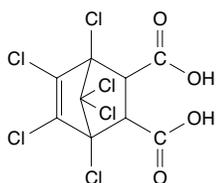
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Chlorendic Acid

CAS No. 115-28-6

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

Chlorendic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chlorendic acid caused tumors in two rodent species and at several different tissue sites. Dietary administration of chlorendic acid caused liver cancer (hepatocellular carcinoma) in female rats and male mice (NTP 1987). In male rats, it caused benign tumors of the liver (adenoma) and pancreas (acinar-cell adenoma); benign lung tumors (alveolar/bronchiolar adenoma) and malignant preputial-gland tumors (carcinoma) may also have been exposure-related.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chlorendic acid.

Properties

Chlorendic acid is structurally related to chlorinated insecticides such as heptachlor, chlordane, endosulfan, endrin, and dieldrin (NTP 1987). It is a white crystalline solid at room temperature. It is slightly soluble in water and in nonpolar organic solvents, but it is readily soluble in methanol, ethanol, and acetone. It emits chlorine when

heated to decomposition (IARC 1990). Physical and chemical properties of chlorendic acid are listed in the following table.

Property	Information
Molecular weight	388.8 ^a
Melting point	208°C to 210°C ^a
Log K_{ow}	2.3 ^a
Water solubility	3.5 g/L at 25°C ^b
Vapor pressure	1.4×10^{-8} mm Hg at 25°C ^a
Dissociation constant (pK_a)	3.1 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Chlorendic acid is used as a flame retardant in polyurethane foams, resins, plasticizers, coatings, epoxy resins, and wool fabrics; in the manufacture of alkyl resins for special paints and inks; in the manufacture of polyester resins with special applications in electrical systems, paneling, engineering plastics, and paint; and in the manufacture of corrosion-resistant tanks, piping, and scrubbers. Chlorendic acid is also used as an extreme-pressure lubricant (NTP 1987, IARC 1990, IPCS 1996, HSDB 2009).

Production

In 1981, U.S. production of chlorendic acid was estimated at 7 million pounds, and imports were about 140,000 lb (NTP 1987). Reported worldwide production of chlorendic acid and anhydride totaled 2 million kilograms (4.4 million pounds) in 1987 (IARC 1990) and 4 million kilograms (8.8 million pounds) in 1996 (IPCS 1996). In 2009, chlorendic acid was produced by two manufacturers in Europe (SRI 2009) and was available from eleven suppliers worldwide, including five U.S. suppliers (ChemSources 2009). No recent reports of U.S. imports or exports specifically of chlorendic acid were found. Reports filed in 1986, 1990, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of chlorendic acid totaled 500,000 lb to 10 million pounds (EPA 2004).

Exposure

The primary route of potential human exposure to chlorendic acid is dermal contact, but inhalation exposure also is possible (HSDB 2009). EPA's Toxics Release Inventory reported annual releases of less than 60 lb to the air from 1995 to 2001; however, one facility reported releases of 420 lb to an off-site hazardous waste landfill and 5 lb to the air in 2002. No releases of chlorendic acid were reported from 2003 to 2006 (TRI 2009). In 2007, 96 lb was released, including 88 lb to off-site management and 8 lb as fugitive air emissions. Releases to the environment can occur from sources other than the direct release of chlorendic acid (IPCS 1996). Chlorendic acid can be released as a result of hydrolytic degradation of polyesters, and it is an oxidation product of numerous pesticides, including endosulfan, chlordane, heptachlor, aldrin, dieldrin, isodrin, and endrin and their metabolites. If released to air, it is expected to exist as a particulate (HSDB 2009). It is subject to photolysis on solid surfaces and in solution, resulting in dechlorination, with a half-life of 16 days on solid surfaces and 5 days in solution (IPCS 1996, HSDB 2009). Chlorendic acid is not expected to volatilize from water or soil; it has a low potential for binding to soil and sediment and is expected to have high mobility in soil. Chlorendic acid has been found in the leachate from landfills at concentrations of up to 455 mg/L and has been identified in at least one hazardous-waste site on the National Priorities List (NTP 1987, IPCS 1996).

Chlorendic acid is manufactured in an essentially closed system, which minimizes potential occupational exposure during the manu-

facturing process (NTP 1987); however, releases may occur from its use (IPCS 1996). When used as a reactive flame-retardant or hardening agent, chlorendic acid bonds covalently to the polymer, reducing the potential for human exposure. Human exposure may also occur through its use as an extreme-pressure lubricant and a chemical intermediate. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 55 workers (classified as Machinery Workers, Except Electrical), including 29 women, potentially were exposed to chlorendic acid (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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Chlorinated Paraffins (C₁₂, 60% Chlorine)

CAS No. 108171-26-2

Reasonably anticipated to be human carcinogens

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Carcinogenicity

Chlorinated paraffins (C₁₂, 60% chlorine) are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chlorinated paraffins (C₁₂, 60% chlorine) caused tumors at several different tissue sites in mice and rats. Administration of chlorinated paraffins by stomach tube increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice of both sexes, the thyroid gland (follicular-cell adenoma and carcinoma) in female mice and rats, and the kidney (tubular-cell adenoma and carcinoma) in male rats. It also caused benign liver tumors (hepatocellular adenoma) in rats of both sexes and possibly mononuclear-cell leukemia in male rats (NTP 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chlorinated paraffins (C₁₂, 60% chlorine). Since chlorinated paraffins were listed in the *Fifth Annual Report on Carcinogens*, a registry-based case-control study of cancer of the liver and biliary tract in auto-workers has been identified (Bardin *et al.* 2005). The case-control study was nested in a cohort study of autoworkers exposed to metalworking fluids. Exposure to specific metalworking fluid components and additives was evaluated, and any exposure to chlorinated paraffins (type not specified) was associated with elevated risk of biliary-tract cancer, based on a small number of cases. No increased risk was found for liver cancer; however, the study included only one exposed worker with liver cancer.

Properties

Chlorinated paraffins are chlorinated long-chain aliphatic compounds. They exist as light-yellow to amber-colored viscous, oily liquids that are usually odorless. The commercial products are complex mixtures that contain paraffins with various carbon-chain lengths and varying chlorine content. The commercial products normally contain stabilizers to inhibit decomposition and may contain isoparaffins (< 1%), aromatic compounds (< 0.1%), and metals as contaminants. Chlorinated paraffins are practically insoluble in water, but many products may be emulsified with water. They are miscible with benzene, chloroform, ether, and carbon tetrachloride, slightly soluble in alcohol, and soluble in most aromatic, aliphatic, and terpene hydrocarbons, ketones, esters, and vegetable and animal oils. Chlorinated paraffins have low volatility and are nonflammable. When heated to decomposition, they emit toxic fumes of hydrochloric acid and other chlorinated compounds. The physical and chemical properties of these chemical mixtures are variable. The octanol-water partition coefficient (log *K*_{ow}) ranges from 4.48 to 7.38 (IPCS 1996, HSDB 2009).

Use

Chlorinated paraffins are used as extreme-pressure-lubricant additives in metalworking fluids; as flame retardants in plastics, rubber, and paints; to improve water resistance of paints and fabrics; and as a secondary plasticizer in polyvinyl chloride. Small amounts are also used in caulks, sealants, adhesives, detergents, inks, finished leather, and other miscellaneous products, and are allowed as an indirect food additive (NTP 1986, CMR 2002, HSDB 2009, FDA 2010). In the United States, about 50% of chlorinated paraffins are used in metalworking fluids, 20% in plastics additives, 12% in rubber, 9% in coatings, 6% in adhesives, caulks, and sealants, and the remaining 3% for miscellaneous purposes (CMR 2002). Chlorinated paraffins have replaced polychlorinated biphenyls as fire-retardant lubricants (NTP 1986). Between 1914 and 1918, large amounts of chlorinated paraffins were used as solvents for dichloramine-T in antiseptic nasal and throat sprays (IPCS 1996).

Production

Commercial production of chlorinated paraffins for use as additives in extreme-pressure lubricants began in the 1930s. Global production reached 250,000 metric tons (over 550 million pounds) in 1978 but declined to 99 million pounds in 1983. In 2002, the two U.S. manufacturers reported an annual production capacity of 140 million pounds. Demand for chlorinated paraffins remained relatively steady from 1983 to 2009, at 96 million to 100 million pounds (NTP 1986, IARC 1990, CMR 2002). In 2009, chlorinated paraffins were produced by 78 manufacturers worldwide, including 2 in the United States, 40 in

China, and 22 in India (SRI 2009). No specific data on U.S. imports or exports of chlorinated paraffins were found.

Exposure

No information on potential human exposure specifically to chlorinated paraffins (C₁₂, 60% chlorine) was found, but information was available on potential human exposure to the class of chlorinated paraffins. The routes of potential human exposure include inhalation, dermal contact, and ingestion, primarily through contamination of foods (IPCS 1996). Because chlorinated paraffins are permitted in adhesives used in food packaging, the general population could be exposed to very low concentrations through ingestion of contaminated food products wrapped in these materials (FDA 2010). Short-chain chlorinated paraffins (SCCPs) (C₁₀ to C₁₃) have also been found in food products contaminated through environmental exposure. In Japan, SCCPs were found in high-lipid-content foods such as dairy products, vegetable oil, salad dressing, and mayonnaise, at a mean concentration of 140 ng/g of wet weight (Bayen *et al.* 2006). The next-most-contaminated Japanese food category was fish and shellfish, with SCCP concentrations of 16 to 18 ng/g of wet weight. The levels in Japanese foods would translate to an average daily intake of 680 ng/kg of body weight for a 1-year-old female infant in Japan (the highest rate reported). In European butter samples, SCCPs were measured at concentrations of 1.2 to 2.7 µg/kg of lipid content. In addition, chlorinated paraffins have been isolated from human tissues, including liver, kidney, and adipose tissue, at concentrations of up to 1.5 mg/kg of wet tissue (most values were < 0.09 mg/kg) (Campbell and McConnell 1980), and from breast milk at concentrations up to 0.8 mg/kg of milk fat (Thomas *et al.* 2006).

Chlorinated paraffins are lipophilic and persistent in the environment. The very low vapor pressure indicates that these compounds will not volatilize easily. If released to air, they will exist as particulates and will not remain in the atmosphere; they may be photochemically degraded, with a half-life of 1.2 to 1.8 days (IPCS 1996). Chlorinated paraffins have been measured in the atmosphere in the United Kingdom at concentrations of up to 3.4 ng/m³ (Barber *et al.* 2005).

Chlorinated paraffins have low water solubility and a high log *K*_{ow}. Therefore, if released to water, they will not volatilize from water or remain in solution, but will adsorb to sediment or suspended solid material. If released to soil, chlorinated paraffins are bound to the soil particles and are not expected to volatilize or to leach into groundwater. Based on limited data, chlorinated paraffins do not biodegrade readily (IPCS 1996, HSDB 2009). In 1988, chlorinated paraffins were measured in the United States in water, sediment, and aquatic organisms downstream from industrial facilities where chlorinated paraffins were made or used. The concentrations measured were less than 8 µg/L in water (compared with < 0.3 µg/L upstream from the same facility) and up to 40 mg/kg in sediment. SCCP concentrations measured in Lake Ontario sediment cores in 1998 averaged 49 µg/kg. Maximum SCCP concentrations in the sediment cores increased from less than 50 µg/kg in 1900 to over 800 µg/kg in the 1980s and then declined to 410 µg/kg in 1998 (Marvin *et al.* 2003). These data are consistent with a maximum concentration of 347 µg/kg in sediment samples collected in the Czech Republic in 2003 (Pribylova *et al.* 2006). In 1980, short- and medium-chain chlorinated paraffins were measured in non-industrialized areas of the United Kingdom at concentrations up to 1 µg/L in water and up to 1 mg/kg in sediment; in industrialized areas, measured concentrations in sediment were as high as 15 mg/kg (Campbell and McConnell 1980). Marine samples collected away from land in the North and Baltic Seas from 2001 to 2003 contained SCCPs at concentrations of up to 377 µg/kg (Huttig and Oehme 2005).

Aquatic organisms were found to contain chlorinated paraffins (C₁₀ to C₂₀) at concentrations similar to those in sediment; for example, a mean concentration of 3.25 mg/kg was found in mussels collected in the United Kingdom (Campbell and McConnell 1980). Chlorinated paraffins potentially may bioaccumulate in some animal species (IPCS 1996, Huttig and Oehme 2005); however, they do not biomagnify in the food chain (Madeley and Birtley 1980). They were also measured in the blubber of marine mammals at concentrations of 0.164 to 1.4 µg/kg and in the fat of terrestrial wildlife at up to 4.4 mg/kg (IPCS 1996).

Occupational exposure is likely in production plants or in industries using chlorinated paraffins (IPCS 1996). In facilities using metalworking fluids containing chlorinated paraffins for milling, cutting, and grinding, aerosol concentrations of up to 1.15 mg/m³ were reported; however, it is not known whether chlorinated paraffin aerosols are in the inhalable size range. Dermal exposure of the hands and forearms was predicted to range from 0.1 to 1 mg/cm² per day for production of chlorinated paraffins and up to 1.5 mg/cm² for their use as metalworking fluids. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 573,193 workers, including 38,354 women, potentially were exposed to substances in the category "Paraffin, chlorinated (CAS 63449-39-8, Paraffin waxes and hydrocarbon waxes)" and that 61,464 workers, including 3,717 women, potentially were exposed to substances in the smaller category of "Chlorinated paraffin" (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chlorinated paraffins are considered marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA)

Chlorinated paraffins are allowed for use as indirect additives used in food contact substances as prescribed in 21 CFR 175 and 177.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 5 mg/m³ for paraffin oil mist.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,500 mg/m³ for paraffin oil mist.
Recommended exposure limit (REL) = 5 mg/m³ for paraffin oil mist.
Short-term exposure limit (STEL) = 10 mg/m³ for paraffin oil mist.

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Chloroform

CAS No. 67-66-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to chloroform caused tumors in two rodent species and at two different tissue sites. Administration of chloroform by stomach tube caused liver cancer (hepatocellular carcinoma) in mice of both sexes (NCI 1976) and kidney tumors (epithelial tumors) in male mice and rats (IARC 1979, Roe *et al.* 1979).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified, which reported that chloroform caused liver and kidney tumors by additional routes of exposure. Benign liver tumors (adenoma) were observed in female rats administered chloroform in the drinking water (IARC 1987, 1999) and female mice exposed by inhalation (Yamamoto *et al.* 2002). Benign and malignant kidney tumors (tubular-cell adenoma, carcinoma, or adenocarcinoma) were observed in male rats exposed via the drinking water (IARC 1987, 1999), male mice exposed by inhalation (Yamamoto *et al.* 2002), and male rats following combined exposure via inhalation and the drinking water (Nagano *et al.* 2006).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chloroform. Two community-based studies of exposure to chlorinated water found excesses of cancer at several tissue sites, particularly the urinary bladder (Cantor *et al.* 1978, Hogan *et al.* 1979), but a causal relationship could not be inferred (IARC 1982).

Since chloroform was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified, mostly involving exposure to chlorinated water, which may contain chloroform and other chlorinated hydrocarbons, via drinking, bathing, showering, or swimming. The International Agency for Research on Cancer (IARC 1999) concluded that a causal relationship between cancer and chloroform could not be inferred, because of the use of indirect methods of assessing exposure, incomplete control for confounding by exposure to other water impurities or other risk factors, and differing results for men and women. Overall, cohort and case-control studies found a relationship between exposure to chlorinated water and the risk of some types of cancer, particularly of the urinary bladder and rectum and possibly of the colon (IARC 1982, 1987, 1999).

Since the last IARC review, additional community-based studies have been identified, which have examined cancer risks associated with estimated exposure to chlorinated drinking water. Several studies, including a pooled analysis of six case-control studies, reported associations of urinary-bladder cancer with overall trihalomethane exposure (Villanueva *et al.* 2004, 2007, Chang *et al.* 2007, Michaud *et al.* 2007); two studies found an exposure-response relationship for men but not women (Villanueva *et al.* 2004, 2007). One study also found an association in men between urinary-bladder cancer and exposure to trihalomethanes via bathing, showering, or swimming in pools (Villanueva *et al.* 2007). Some studies also reported associations between colorectal cancer and overall trihalomethane exposure (King *et al.* 2000, Kuo *et al.* 2009, 2010). Few studies of drinking-water exposure attempted to distinguish the risk associated specifically with exposure to chloroform, and none controlled adequately for exposure to other trihalomethanes or other risk factors. However, one study found a significantly elevated risk of urinary-bladder cancer associated with high levels of chloroform in drinking water (Bove *et al.* 2007).

Properties

Chloroform is a trihalomethane that exists at room temperature as a clear, colorless, highly refractive heavy liquid with a pleasant ethereal odor (Akron 2009, HSDB 2009). It is slightly soluble in water, soluble in carbon disulfide, and miscible with alcohol, ether, benzene, carbon tetrachloride, and fixed and volatile oils (HSDB 2009). Chloroform is stable under normal temperatures and pressures in a closed container (Akron 2009). It is light sensitive and may decompose slowly in the presence of sunlight and in the dark in the presence of air (IARC 1979). Physical and chemical properties of chloroform are listed in the following table.

Property	Information
Molecular weight	119.4 ^a
Specific gravity	1.4888 at 25°C/25°C ^a
Melting point	-63.41°C ^a
Boiling point	61.2°C ^a
Log K _{ow}	1.97 ^a
Water solubility	7.950 g/L at 25°C ^b
Vapor pressure	197 mm Hg at 25°C ^a
Vapor density relative to air	4.12 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

In 2007, about 95% of the chloroform produced in the United States was used to make chlorodifluoromethane (HCFC-22, also known as R-22); 62% of HCFC-22 was used as a refrigerant, and 33% was used in the production of fluoropolymers (HSDB 2009). However, the use of HCFC-22 is being phased out under the 1987 Montreal Protocol, and as of January 1, 2010, manufacturers were not allowed to pro-

duce new air conditioners or heat pumps containing HCFC-22 (EPA 2010). The remaining chloroform produced has miscellaneous uses, including as a solvent or an extraction solvent for lacquers, floor polishes, adhesives in artificial silk manufacturing, resins, fats, greases, gums, waxes, oils, alkaloids, penicillin, vitamins, flavors, and rubber; as a drycleaning spot remover; in fire extinguishers; as an intermediate in the preparation of dyes and pesticides; and as a fumigant for stored grain crops (IARC 1979, ATSDR 1997, HSDB 2009). It may also be used as a local anesthetic in certain dental endodontic surgeries and in aspirin-chloroform mixtures applied topically to relieve pain from severe cases of herpes or post-therapeutic neuralgia (ATSDR 1997, HSDB 2009).

Before 1976, chloroform was used in a wide variety of drug products, including cough syrups, antihistamines, and decongestants (IARC 1979). In the 1970s, the U.S. Food and Drug Administration banned drugs containing chloroform and also banned its use in cosmetics because of its carcinogenicity. However, it did not ban drug products that contain chloroform in residual amounts resulting from its use as a solvent in manufacturing or its presence as a by-product from the synthesis of drug ingredients (IARC 1979, ATSDR 1997). An approved new drug application is required for marketing any drug product containing chloroform (FDA 1999).

Production

One U.S. manufacturer began chloroform production in 1903, but commercial production was not reported until 1922 (IARC 1979). From the early 1980s to the mid 1990s, the annual production of chloroform increased by 20% to 25%, primarily because of the great demand for the refrigerant HCFC-22 (ATSDR 1997). In 2004, annual U.S. production capacity at four manufacturing facilities was 765 million pounds (CMR 2004). In 2009, chloroform was produced by 40 manufacturers worldwide, 4 of which were in the United States (SRI 2009), and was available from 105 suppliers, including 42 U.S. suppliers (ChemSources 2009). U.S. imports of chloroform decreased from a high of 17.3 million kilograms (38 million pounds) in 1989 to a low of 44,000 kg (97,000 lb) in 1997 and have since fluctuated; in 2008, imports totaled 180,000 kg (0.4 million pounds). U.S. exports of chloroform increased from 15 million kilograms (33.5 million pounds) in 1985 to 180 million kilograms (396 million pounds) in 2004 and have since been variable, decreasing to 120 million kilograms (264 million pounds) in 2008 (USITC 2009).

Exposure

The routes of potential human exposure to chloroform are ingestion, inhalation, and dermal contact (HSDB 2009). Exposure to chlorinated water is expected to be a primary source of human exposure to chloroform, because many public water supplies and swimming pools contain trihalomethanes as by-products of chlorination for disinfection purposes. Chloroform is the most prevalent trihalomethane in treated water. Most exposure of the general population occurs during the use of chlorine-treated water (e.g., for showering, swimming, cleaning, drinking, or cooking) (IARC 1979, 1999, ATSDR 1997, HSDB 2009). Chloroform's concentration in water systems is not constant over time or location, because trihalomethane concentrations increase with the length of time the water remains in the distribution system (Ashley *et al.* 2005). Typical daily levels of adult exposure to chloroform from drinking water are estimated to range from 0.199 to 1.89 $\mu\text{g}/\text{kg}$ of body weight (WHO 2004). Foods such as dairy products, oils and fats, vegetables, bread, and beverages may also contain small amounts of chloroform (IARC 1999, HSDB 2009), resulting in an estimated average daily intake of 0.043 to 0.478 $\mu\text{g}/\text{kg}$ of body weight for adults aged 20 to 59 years (IPCS 2004).

Chloroform is also present in the ambient air, surface water, ground water, and soil. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chloroform declined steadily from about 28 million pounds in 1988 to 706,555 lb in 2007, when it was released from 67 facilities (TRI 2009). Chloroform has been detected in the atmosphere at concentrations ranging from 0.10 to 10.0 $\mu\text{g}/\text{m}^3$ in urban areas in the United States and in indoor air at 0.17 to 43.9 $\mu\text{g}/\text{m}^3$ (IPCS 2004). It has also been measured in surface water in rivers, lakes, and oceans, and in precipitation. The highest concentration recently measured in a U.S. river was 2.1 $\mu\text{g}/\text{L}$ (McCulloch 2003). In open oceans and estuaries, the highest reported concentration was 70 $\mu\text{g}/\text{L}$ in the estuary of the Mersey River, in England (Zok *et al.* 1998). Chloroform has also been measured in snowpack in the Antarctic, Italy, and Germany, at a maximum concentration of 380 ng/kg (0.00038 mg/kg) in Antarctic snow (Zoccolillo *et al.* 2007). Contamination of groundwater by chloroform was found at the site of a plutonium processing facility near Knoxville, Tennessee, at a mean concentration of 0.108 mg/L (Datskou and North 1996). Chloroform was measured at 1.1 mg/kg in soil samples taken from a small garden in Spain irrigated with chlorine-treated tap water (Campillo *et al.* 2004).

If exposure to chloroform through inhalation of ambient air and indoor air and through ingestion of food are added to exposure through ingestion of drinking water, daily adult exposure is estimated to range from 0.70 $\mu\text{g}/\text{kg}$ to over 3.0 $\mu\text{g}/\text{kg}$ of body weight. Exposure due to daily showering (inhalation and dermal) alone is estimated to add 0.36 to 3.4 $\mu\text{g}/\text{kg}$. Two studies reported changes in chloroform concentrations in the blood as a result of household water use, including showering, bathing, and hand washing of dishes (Ashley *et al.* 2005, Nuckols *et al.* 2005). The concentration of chloroform in the blood increased 2- to 7-fold after showering; at two study sites, the median water concentrations of chloroform were 8 and 85 ppb, and the median blood concentrations after showering were 57 and 280 ppt (ng/L) (Nuckols *et al.* 2005). Ingestion of drinking water caused little elevation in blood levels of chloroform; however, the use of hot water during showering, bathing, and hand washing of dishes caused significant peaks in chloroform blood concentrations. Dermal absorption of chloroform is affected by water temperature during bathing. Among 10 subjects, the mean amount of chloroform exhaled was 0.2 μg at the lowest bath-water temperature (30°C) and 7 μg at the highest temperature (40°C), for a 35-fold increase (Gordon *et al.* 1998).

Several studies have shown that inhalation and dermal exposure to chloroform are important during swimming. Lindstrom *et al.* (1997) measured dermal and inhalation exposure to chloroform from swimming in a chlorinated pool; two college students (one male and one female) were monitored during a typical two-hour workout. The mean concentration of chloroform in their breath was as high as 371 $\mu\text{g}/\text{m}^3$ and 339 $\mu\text{g}/\text{m}^3$, over twice the maximum possible concentration from inhalation exposure only. Furthermore, the maximum alveolar breath concentrations ultimately reached over twice the ambient indoor chloroform concentration, suggesting that dermal absorption was more important than inhalation. The dermal contribution was estimated at over 90% of total exposure. Other studies found that inhalation exposure to chloroform resulted in 80% absorption. Placental transfer of chloroform also has been demonstrated (IPCS 2004).

Occupational exposure may occur during the manufacture or use of chloroform (ATSDR 1997). Workers at wastewater and other treatment plants can be exposed to significant levels of chloroform. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 95,772 workers, including 41,394 women,

in 20 industrial categories potentially were exposed to chloroform (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Chloroform is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 20,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clear Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 5.7 µg/L; based on fish or shellfish consumption only = 470 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 6.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chloroform = U044, F024, F025, K009, K010, K019, K020, K021, K029, K073, K116, K149, K150, K151, K158.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.080 mg/L for the sum of chloroform, bromodichloromethane, dibromochloromethane, and bromoform.

Food and Drug Administration (FDA)

All drug products containing chloroform have been removed from the market, and a new drug application is required for approval.

Chloroform may not be used as an ingredient in cosmetic products.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Ceiling concentration = 50 ppm (240 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Short-term exposure limit (STEL) = 2 ppm (9.78 mg/m³) (60-min exposure).

Immediately dangerous to life and health (IDLH) limit = 500 ppm.

Listed as a potential occupational carcinogen.

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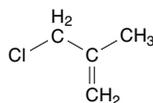
3-Chloro-2-methylpropene

CAS No. 563-47-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as 3-chloro-2-methyl-1-propene



Carcinogenicity

3-Chloro-2-methylpropene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 3-chloro-2-methylpropene caused tumors in two rodent species and at several different tissue sites. Administration of 3-chloro-2-methylpropene by stomach tube caused benign or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma) in mice and rats of both sexes; in mice, some of the malignant tumors metastasized to other organs. Kidney and urinary-bladder tumors in male rats may also have been related to 3-chloro-2-methylpropene exposure.

Since 3-chloro-2-methylpropene was listed in the *Fifth Annual Report on Carcinogens*, an additional study in mice has been identified. Inhalation exposure to 3-chloro-2-methylpropene caused benign forestomach tumors (squamous-cell papilloma) in mice of both sexes and benign Harderian-gland tumors (adenoma) in female mice (Katagiri *et al.* 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3-chloro-2-methylpropene.

Properties

3-Chloro-2-methylpropene exists at room temperature as a colorless to straw-colored liquid with a sharp, disagreeable odor. It is slightly soluble in water, soluble in acetone, very soluble in chloroform, and miscible with ethanol and diethyl ether. It can polymerize on exposure to light and is explosively flammable. The vapors are heavier than air and may travel from the source and collect in low or confined areas (IARC 1995, Akron 2009, HSDB 2009). Physical and chemical properties of 3-chloro-2-methylpropene are listed in the following table.

Property	Information
Molecular weight	90.6 ^a
Specific gravity	0.92 at 20°C/4°C ^a
Melting point	< -80°C ^a
Boiling point	71°C to 72°C ^a
Log <i>K</i> _{ow}	2.48 ^b
Water solubility	1.4 g/L at 25°C ^b
Vapor pressure	101.7 mm Hg at 20°C ^a
Vapor density relative to air	3.1 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

3-Chloro-2-methylpropene is used primarily as a chemical intermediate in the production of organic chemicals, including 3-dimethylamino-2-methylpropyl chloride hydrochloride, 2-methyl-epichlorohydrin, and the pesticides carbofuran, ethalfuralin, and fenbutatin oxide. In 1985, over 97% of its production was used as an intermediate in the production of agricultural chemicals; the remainder was used as a textile or perfume additive or for other purposes. Outside of the United States, 3-chloro-2-methylpropene has been used as an insecticide fumigant for grains, tobacco, and soil; however, it is not registered for use as a pesticide in the United States (NTP 1986, IARC 1995, HSDB 2009).

Production

In 1984, U.S. production of 3-chloro-2-methylpropene was estimated at 12 million to 24 million pounds (NTP 1986). In 2009, 3-chloro-2-methylpropene was produced by one manufacturer worldwide, in China (SRI 2009), and was available from 18 suppliers, including 9 U.S. suppliers (ChemSources 2009). Reports filed in 1986, 1990, 1998, 2002, and 2006 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 3-chloro-2-methylpropene totaled 10 million to 50 million pounds; in 1994, the quantity was 1 million to 10 million pounds (EPA 2004, 2009).

Exposure

The primary routes of potential human exposure to 3-chloro-2-methylpropene are inhalation, ingestion, and dermal contact. Use as a fumigant would result in the direct release of 3-chloro-2-methylpropene to the environment; however, this use has not been reported in the United States (HSDB 2009). Consumers could be exposed through ingestion of food products that had absorbed 3-chloro-2-methylpropene (NTP 1986). According to EPA's Toxics Release Inventory, environmental releases of 3-chloro-2-methylpropene in 1996 and 1997 totaled 26,000 lb. In 2007, one facility released 6,536 lb to air (TRI 2009). If released to air, 3-chloro-2-methylpropene will exist only in the vapor phase and be degraded by reaction with hydroxyl radicals, with an estimated half-life of 10 hours, and with ozone, with an estimated half-life of 27 hours (HSDB 2009). If released to water, 3-chloro-2-methylpropene will volatilize, with an estimated half-life of 3 hours in a model river and 4 days in a model lake. If released to soil, it is expected to volatilize and to have high mobility. It is not expected to bind to soil or sediments. It is expected to biodegrade under aerobic conditions and to have a low potential for bioaccumulation. Around 1980, 3-chloro-2-methylpropene was detected in the ambient air in an industrial area near Curtis Bay, Maryland, at concentrations of up to 400 µg/m³ (NTP 1986).

Occupational exposure to 3-chloro-2-methylpropene may occur during its manufacture or use as an intermediate in organic synthesis. No data on occupational exposure were found.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of 3-chloro-2-methylpropene is subject to certain provisions for the control of volatile organic compound emissions.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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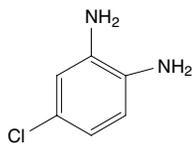
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 3-Chloro-2-Methyl-1-Propene. Last accessed: 8/11/09.

4-Chloro-*o*-phenylenediamine

CAS No. 95-83-0

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

4-Chloro-*o*-phenylenediamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4-chloro-*o*-phenylenediamine caused tumors in two rodent species and at several different tissue sites. Dietary administration of technical-grade 4-chloro-*o*-phenylenediamine caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and benign or malignant tumors of the urinary bladder and forestomach (papilloma or carcinoma) in rats of both sexes (NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4-chloro-*o*-phenylenediamine.

Properties

4-Chloro-*o*-phenylenediamine is a chlorinated aromatic amine that exists as a brown crystalline solid or powder at room temperature (Akron 2009). It is slightly soluble in water, but it is soluble in benzene and very soluble in ethanol and ether. 4-Chloro-*o*-phenylenediamine is stable at normal temperatures and pressures. Physical and chemical properties of 4-chloro-*o*-phenylenediamine are listed in the following table.

Property	Information
Molecular weight	142.6 ^a
Melting point	76°C ^a
Boiling point	229°C ^b
Log K _{ow}	1.28 ^a
Water solubility	6.6 g/L at 25°C ^b
Vapor pressure	2.06 × 10 ⁻³ mm Hg 25°C ^b
Dissociation constant (pK _a)	3.83 at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

4-Chloro-*o*-phenylenediamine can be used as an oxidation base for dye preparation, as a chemical intermediate to produce 5-chlorobenzotriazole, as a curing agent for epoxy resins, as a reagent in gas chromatography, and to synthesize experimental pharmaceuticals. It has been used as a chemical intermediate in dye production and was patented as a hair-dye component, but there is no evidence that it is currently used in the United States for these purposes (IARC 1982, HSDB 2009).

Production

4-Chloro-*o*-phenylenediamine was first produced commercially in the United States in 1941 (IARC 1982). In 2009, 4-chloro-*o*-phenylenediamine was produced by three manufacturers worldwide, including one in India and two in Europe (SRI 2009), and was available from 20 suppliers worldwide, including 9 U.S. suppliers (ChemSources 2009). U.S. production in 1977 was estimated at 1,000 to 10,000 lb (IARC 1982). No data on U.S. imports or exports of 4-chloro-*o*-phenylenediamine were found. Under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule, U.S. production plus imports totaled 10,000 to 500,000 lb in 1986 (EPA 2004); no later inventory update reports were filed.

Exposure

Because of its limited use in consumer products, little exposure of the general population to 4-chloro-*o*-phenylenediamine is expected. Nevertheless, exposure could potentially occur if residues were present in hair dyes or in products made from 5-chlorobenzotriazole (IARC 1982, HSDB 2009). The primary routes of potential human exposure to 4-chloro-*o*-phenylenediamine are ingestion, inhalation, and dermal contact by workers in the dye and chemical industries and those involved in pharmaceutical research (NCI 1978). Exposure could occur during production and use of 4-chloro-*o*-phenylenediamine or following accidental releases. No data were found on the numbers of workers potentially exposed to 4-chloro-*o*-phenylenediamine.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 4-chloro-*o*-phenylenediamine were identified.

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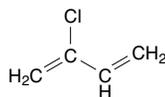
Chloroprene

CAS No. 126-99-8

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Also known as 2-chloro-1,3-butadiene



Carcinogenicity

Chloroprene is *reasonably anticipated to be a human carcinogen* based on evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Inhalation exposure to chloroprene caused tumors at several different tissue sites in mice and rats. It caused lung tumors (alveolar/bronchiolar adenoma and/or carcinoma) in mice of both sexes and in male rats; kidney tumors in rats of both sexes and in male mice (renal-tubule adenoma); and mammary-gland tumors in female rats (fibroadenoma) and mice. In rats of both sexes, it also caused tumors of the oral cavity (squamous-cell papilloma and carcinoma) and thyroid gland (follicular-cell adenoma or carcinoma). In mice, it also caused tumors of the forestomach (squamous-cell papilloma), Harderian gland (adenoma or carcinoma), and blood vessels (hemangioma and hemangiosarcoma) in both sexes and tumors of the liver (hepatocellular adenoma and carcinoma), Zymbal gland (carcinoma), skin (sarcoma), and mesentery (sarcoma) in females (NTP 1998).

Cancer Studies in Humans

Data from two early epidemiological studies suggested that occupational exposure to chloroprene may increase the risks of cancer of the liver, lung, and digestive and lymphohematopoietic systems (Pell 1978, Li *et al.* 1989). Since chloroprene was listed in the *Ninth Report on Carcinogens*, additional epidemiological studies have been identified. Mortality from leukemia and liver cancer was significantly increased among shoe-manufacturing workers, and liver-cancer incidence and mortality were significantly increased among chloroprene-production workers (Bulbulyan *et al.* 1998, 1999). However, two other cohort studies of chloroprene-production workers found no excess

of liver cancer (Colonna and Laydevant 2001, Marsh *et al.* 2007a,b). These two studies reported increased risks of lung or respiratory cancer; however, the risk estimates were not statistically significant or related to exposure category in the small cohort study (Colonna and Laydevant 2001) and were significantly elevated in only one of several plants in the large multi-plant study (Marsh *et al.* (2007a,b).

Studies on Mechanisms of Carcinogenesis

Chloroprene (the 2-chloro analogue of 1,3-butadiene) caused all of the same types of tumors that 1,3-butadiene caused in mice except for lymphoma and tumors of the preputial gland and ovary (NTP 1998).

In vitro metabolism of chloroprene by mouse, rat, hamster, and human microsomes produced (1-chloroethenyl)oxirane, an epoxide that is thought to react with DNA and can be further metabolized by hydrolysis and glutathione conjugation (Himmelstein *et al.* 2001). However, many studies on the genotoxicity of chloroprene have given negative results, and positive results from earlier studies were attributed to differences in the age and purity of the chloroprene samples (Westphal 1994, NTP 1998). The mutagenicity of chloroprene in bacteria (Bartsch *et al.* 1975, 1979) was considered to be due to cyclic dimers that accumulate in aged samples (Westphal *et al.* 1994).

At the same exposure concentrations as used in the inhalation-exposure studies of cancer in mice, chloroprene did not cause sister chromatid exchange or chromosomal aberrations in mouse bone-marrow cells, nor did it increase the frequency of micronucleated erythrocytes in peripheral blood (Tice *et al.* 1988). During another inhalation-exposure study in mice and rats, chloroprene caused dominant lethal mutations in both species and chromosomal aberrations in mouse bone marrow cells (Sanotskii 1976). However, despite the largely negative findings for genotoxicity, chloroprene-induced lung and Harderian-gland tumors from mice had a high frequency of unique mutations of the *K-ras* proto-oncogene (NTP 1998). In addition, occupational-exposure studies reported increased frequencies of chromosomal aberrations in the lymphocytes of workers (IARC 1979).

Properties

Chloroprene is a halogenated alkene that exists at room temperature as a clear colorless liquid with a pungent ether-like odor. It is practically insoluble in water, soluble in alcohol, and miscible with acetone, benzene, and ethyl ether. It is highly flammable and polymerizes on standing, making it unstable in the environment (Akron 2009). Physical and chemical properties of chloroprene are listed in the following table.

Property	Information
Molecular weight	88.5 ^a
Specific gravity	0.956 at 20°C/4°C ^a
Melting point	-130°C ^a
Boiling point	59°C ^a
Log <i>K</i> _{ow}	2.53 ^b
Water solubility	0.875 g/L at 25°C ^b
Vapor pressure	215 mm Hg at 25°C ^a
Vapor density relative to air	3 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The only commercial use identified for chloroprene is as a monomer in the production of the elastomer polychloroprene (neoprene), a synthetic rubber used in the production of automotive and mechanical rubber goods, adhesives, caulks, flame-resistant cushioning, construction materials, fabric coatings, fiber binding, and footwear. Other uses of this polymer include applications requiring chemical, oil, or weather resistance or high gum strength. The U.S. Food and

Drug Administration permits the use of chloroprene as a component of adhesives used in food packaging and also permits the use of polychloroprene in products intended for use with food (IARC 1979, 1999, NTP 1998).

Production

In 2009, chloroprene was produced by one manufacturer each in the United States and China and two manufacturers in Europe (SRI 2009) and was available from eleven suppliers, including seven U.S. suppliers (ChemSources 2009). Reports filed between 1986 and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of chloroprene totaled 100 million to 500 million pounds (EPA 2004).

Exposure

The routes of human exposure to chloroprene are inhalation, ingestion, and dermal contact. Chloroprene is not known to occur naturally in the environment (IARC 1999). The main sources of environmental releases are effluent and emissions from facilities that use chloroprene to produce polychloroprene elastomers. According to EPA's Toxics Release Inventory, environmental releases of chloroprene have decreased steadily from a high of over 2 million pounds in 1988 (the year reporting started). In 2007, two facilities reported chloroprene releases of over 275,000 lb, and seven facilities reported releases of 1,300 lb or less, almost all to air (TRI 2009). When released to air, chloroprene reacts with photochemically generated hydroxyl radicals, with a half-life of 18 hours, and smaller amounts are removed by reaction with ozone, with a half-life of 10 days. Based on the Henry's law constant and octanol-water partition coefficient, chloroprene is expected to be removed from water and damp soil primarily by volatilization. If released to water, chloroprene is expected to volatilize from the surface, with a half-life of 3 hours from streams and 4 days from lakes. It will not adsorb to sediment or suspended solids or bioaccumulate in aquatic organisms. If released to soil, chloroprene is expected to volatilize or may leach into groundwater (HSDB 2009). In 1991, EPA's Urban Air Toxics Monitoring Program identified chloroprene in 88 of 349 samples (25.2%), at concentrations ranging from 0.01 to 1.78 ppb (0.036 to 6.44 $\mu\text{g}/\text{m}^3$). The results were similar in 1996, but in 2000 and 2005, chloroprene was detected in only one sample.

The main source of occupational exposure to chloroprene is the manufacture of chloroprene or polychloroprene (NTP 1998). In 1977, it was estimated that 2,500 to 3,000 workers were exposed to chloroprene during its manufacture and polymerization (Infante 1977). Chloroprene monomer is manufactured in a closed system, which is then used on site to make the polymer. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 17,700 workers, including 650 women, potentially were exposed to chloroprene or polychloroprene (NIOSH 1990). Time-weighted 8-hour average concentrations at three facilities (two in the United States and one in Northern Ireland) from 1975 to 1992 were 1 ppm in all but three samples, and chloroprene concentrations in the monomer manufacturing phase were below 1.8 ppm in all samples (Hall *et al.* 2007). During the polymer manufacturing phase, chloroprene concentrations were as high as 4.66 ppm in Northern Ireland and 3.42 ppm in the United States. By 1992, concentrations in all polymer facilities were lower (1.4 and 0.53 ppm in the United States and 0.37 ppm in Northern Ireland).

Regulations

Department of Transportation (DOT)

Chloroprene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 25 ppm (90 mg/m^3).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm (36 mg/m^3).

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 1 ppm (3.6 mg/m^3) (15-min exposure).
Immediately dangerous to life and health (IDLH) limit = 300 ppm (1,086 mg/m^3).
Listed as a potential occupational carcinogen.

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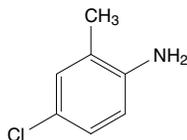
p-Chloro-*o*-toluidine and Its Hydrochloride

CAS Nos. 95-69-2 and 3165-93-3

Reasonably anticipated to be human carcinogens

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 4-chloro-*o*-toluidine or 4-chloro-2-methylaniline



Carcinogenicity

p-Chloro-*o*-toluidine and its hydrochloride salt are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of *p*-chloro-*o*-toluidine from epidemiological studies in humans. Three cohort studies found high relative risks for urinary-bladder cancer among workers exposed to *p*-chloro-*o*-toluidine; however, confounding by co-exposure to other potential urinary-bladder carcinogens could not be ruled out. Documented human exposure to *p*-chloro-*o*-toluidine has occurred primarily in the dye and synthetic-chemical industries (IARC 2000). Between 1982 and 1990, 7 cases of urinary-bladder cancer were detected in a group of 49 German and Danish workers who were involved in producing the insecticide chlordimeform from *p*-chloro-*o*-toluidine on an irregular basis for an average of 18 years (Popp *et al.* 1992). The incidence of urinary-bladder tumors in this group was significantly higher than the expected incidence based on national or regional cancer registries. A brain tumor also occurred in one of the seven workers with urinary-bladder cancer. Exposure levels were not documented, but exposure to *p*-chloro-*o*-toluidine from 1980 to 1986 was demonstrated analytically by monitoring of the workers' urine, where it was reported to be present at minimal levels (concentrations were not reported). There was

some evidence that the cohort handled other chemicals (including *o*-chloroaniline); however, none of the resulting exposures were quantified by chemical analysis at the time. In other studies, workers were exposed to *p*-chloro-*o*-toluidine and numerous other compounds, several of which are potential carcinogens. No exposure levels were documented, and the exposures occurred before 1980, when modern industrial-hygiene standards were implemented (Ott and Langner 1983, Stasik 1988, IARC 1990, Hogan 1993).

Cancer Studies in Experimental Animals

Dietary administration of *p*-chloro-*o*-toluidine hydrochloride caused benign or malignant blood-vessel tumors (hemangioma or heman-giosarcoma) in the spleen and adipose tissue in mice of both sexes, in two different mouse strains (Weisburger *et al.* 1978, NCI 1979, IARC 1990).

Studies on Mechanisms of Carcinogenesis

p-Chloro-*o*-toluidine caused genetic damage in a variety of prokaryotic and mammalian *in vitro* and *in vivo* test systems (IARC 1990, Goggelmann *et al.* 1996). *p*-Chloro-*o*-toluidine binding to DNA was demonstrated *in vitro* with calf thymus DNA and *in vivo* following administration to mice and rats by intraperitoneal injection (Hill *et al.* 1979, Bentley *et al.* 1986, IARC 2000). In organs from animals exposed to *p*-chloro-*o*-toluidine, DNA breakage was detected by single-cell gel electrophoresis (comet assay) in mouse liver, urinary bladder, lung, and brain and in rat liver and kidney (Sekishashi *et al.* 2002).

Properties

p-Chloro-*o*-toluidine is a chlorinated aromatic amine that exists as a grayish-white crystalline solid or leaflet, and *p*-chloro-*o*-toluidine hydrochloride is a buff-colored or light-pink powder at room temperature. The base compound is practically insoluble in water or carbon tetrachloride but is soluble in ethanol or dilute acid solutions. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of *p*-chloro-*o*-toluidine are listed in the following table. No physical and chemical properties for the hydrochloride were found except its molecular weight of 178.1 and melting range of 265°C to 270°C (IARC 2000, Weisburger 1978).

Property	Information
Molecular weight	141.6 ^a
Melting point	30°C ^a
Boiling point	241°C ^a
Log <i>K</i> _{ow}	2.27 ^b
Water solubility	0.95 g/L at 25°C ^b
Vapor pressure	0.041 mm Hg at 25°C ^b
Vapor density relative to air	4.9 ^a
Dissociation constant (p <i>K</i> _a)	3.85 at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

p-Chloro-*o*-toluidine and its hydrochloride salt are used in manufacturing azo dyes for cotton, silk, acetate, and nylon and as intermediates in the production of the dyes C.I. 12800, pigment red 7, and pigment yellow 49 (IARC 1990, 2000). *p*-Chloro-*o*-toluidine has also been used since the 1960s in the manufacture of the pesticide (insecticide and acaricide) chlordimeform. It is believed that chlordimeform is no longer produced or used worldwide (IARC 1990).

Production

Commercial production of *p*-chloro-*o*-toluidine began in Germany in 1924 and was first reported in the United States in 1939 (IARC 1990, 2000). In 2009, *p*-chloro-*o*-toluidine was produced by

two manufacturers in China and one in India (SRI 2009); worldwide, *p*-chloro-*o*-toluidine free base was available from 25 suppliers and the hydrochloride from 5 suppliers (ChemSources 2009). In 1976, U.S. imports of the free base were 25,000 lb (NCI 1979). U.S. imports in a category of substances including *p*-chloro-*o*-toluidine (toluidines and their salts) were 680,000 kg (1.5 million pounds) in 1995, reached a high of 708,000 kg (1.6 million pounds) in 2000, and declined to 209,000 kg (461,000 lb) in 2004. No imports in this category were reported from 1989 to 1994. From 1989 to 2004, U.S. exports in this category ranged from a high of 9.8 million kilograms (22 million pounds) in 1992 to a low of 1.8 million kilograms (3.7 million pounds) in 2002 (USITC 2009). Reports filed in 1986 and 1990 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *p*-chloro-*o*-toluidine totaled 10,000 to 500,000 lb. No inventory update reports for *p*-chloro-*o*-toluidine were filed in 1994 or 1998, and reports in 2002 indicated a quantity of less than 10,000 lb (EPA 2004).

Exposure

The routes of potential human exposure to *p*-chloro-*o*-toluidine are inhalation, ingestion, and dermal contact. The general population can be exposed to *p*-chloro-*o*-toluidine from the use of products that contain it as an impurity; for example, *p*-chloro-*o*-toluidine was found in five samples of finger paints tested in a study in Spain (Garrigos *et al.* 2000). *p*-Chloro-*o*-toluidine hydrochloride has also been found as an impurity in the pesticide chlordimeform (IARC 2000).

p-Chloro-*o*-toluidine could be released to the environment from decomposition of chlordimeform. As of 2000, chlordimeform was not believed to be produced or used anywhere in the world (IARC 2000). Previously, *p*-chloro-*o*-toluidine was isolated and identified in field samples of plant materials treated with chlordimeform. It was measured in young bean leaves at concentrations of less than 0.1 to 0.2 ppm (mg/kg), in grape stems at 0.02 to 0.3 ppm, in a mixture of grape stems and berries at 0.02 to 0.05 ppm, and in prunes and apples at less than 0.04 ppm (Kossmann *et al.* 1971). *p*-Chloro-*o*-toluidine was also reported to be metabolized from chlordimeform by enzymes present in the leaves of apple seedlings and in cotton plants (IARC 1990, 2000). In an experimental field application, residual concentrations of *p*-chloro-*o*-toluidine were found in rice grains at 3 to 61 ppb ($\mu\text{g}/\text{kg}$), in straw parts at 80 to 7,200 ppb, in the upper layer of soil (0 to 5 cm) at 2 to 68 ppb, and in the lower layer of soil (5 to 10 cm) at trace levels to 20 ppb. In another experimental field application of chlordimeform, no residues of *p*-chloro-*o*-toluidine were detected in rice grains or husks tested 20 to 55 days after pesticide application (IARC 1990). Mammals (including dogs, rats, goats, and humans) also metabolize chlordimeform to *p*-chloro-*o*-toluidine.

If *p*-chloro-*o*-toluidine is released to air, it will exist as a vapor and degrade by direct photolysis or photochemically produced hydroxyl radicals, with an estimated half-life of 9 hours. If it is present in water, it will slowly volatilize. It is expected to be moderately mobile in mainly inorganic soils but to bind tightly to soils with high humus or organic-matter content. *p*-Chloro-*o*-toluidine will biodegrade slowly in soil or water and has a low potential for bioaccumulation (HSDB 2009).

p-Chloro-*o*-toluidine has been measured in the urine of workers exposed to chlordimeform; however, no data were found on the levels detected (IARC 1983, 1990). Occupations with the greatest potential for exposure to *p*-chloro-*o*-toluidine include manufacturers of pigments, dyes, and chlordimeform (IARC 2000). Exposures to *p*-chloro-*o*-toluidine were reported to occur during the charging of mixing vats and at the basification stage at a chemical purification facility in England, at a batch-operated chemical processing plant

in the United States, and during its production and processing at a facility in Germany. Data on exposure levels were not provided for any of these studies (IARC 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 250 workers (health-services workers and chemists, but not biochemists), all of whom were women, potentially were exposed to *p*-chloro-*o*-toluidine and that 682 workers (health-services and clinical-laboratory workers and health aides, but not nursing aides), including 425 women, potentially were exposed to *p*-chloro-*o*-toluidine hydrochloride (NIOSH 1990b).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 100 lb for *p*-chloro-*o*-toluidine hydrochloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: *p*-Chloro-*o*-toluidine is a listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *p*-chloro-*o*-toluidine hydrochloride = U049.

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Chromium Hexavalent Compounds

CAS No. 18540-29-9

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Chromium hexavalent (VI) compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies in various geographical locations have consistently reported increased risks of lung cancer among workers engaged in chromate production, chromate pigment production, and chromium plating. Epidemiological studies of lung cancer among ferrochromium workers were inconclusive. Exposure to specific chromium compounds varies by industry. Chromate-production workers are exposed to a variety of chromium compounds, including hexavalent (VI) and trivalent (III) compounds. Chromate-pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds. Epidemiological studies of stainless-steel welders exposed to chromium(VI) compounds also found an increased risk of lung cancer; however, these studies are of limited use for evaluation of chromium's carcinogenicity, because the welders were also exposed to other potential carcinogens. In addition, epidemiological studies of chromate production workers, chromate pigment workers, and chrome platers found an increased risk of a rare cancer of the sinonasal cavity. The data for cancer at sites other than the lung and sinonasal cavity were unclear. The International Agency for Research on Cancer concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds as encountered in the chromate-production, chromate-pigment-production, and chromium-plating industries (IARC 1973, 1979, 1990).

Cancer Studies in Experimental Animals

Exposure to chromium(VI) compounds (calcium chromate, chromium trioxide, or sodium dichromate) via inhalation or intratracheal or intrabronchial implantation caused benign and/or malignant lung tumors in rats and/or mice. Intrabronchial implantation of zinc chromate or strontium chromate also caused bronchial tumors in rats, and inhalation exposure to chromium trioxide caused benign nasal tumors in mice. In addition, cancer at the injection site was observed in rats following administration of chromium compounds (calcium chromate, lead chromate, basic lead chromate, zinc chromate, or

strontium chromate) by intrapleural, subcutaneous, or intramuscular injection and in mice following intramuscular injection of calcium chromate (IARC 1980, 1990). IARC (1990) concluded that there was sufficient evidence in experimental animals for the carcinogenicity of calcium chromate, lead chromates, strontium chromate, and zinc chromates and limited evidence for the carcinogenicity of chromium trioxide and sodium dichromate.

Since chromium hexavalent compounds were reviewed for listing in the *First Annual Report on Carcinogens* and reviewed by IARC in 1990, the National Toxicology Program has conducted two-year cancer studies of sodium dichromate in rats and mice. Sodium dichromate administered in the drinking water caused cancer of the oral cavity (squamous-cell carcinoma of the oral mucosa) in rats and increased the combined incidence of benign and malignant tumors (adenoma and carcinoma) of the small intestine (duodenum, jejunum, or ileum) in mice (NTP 2008).

Studies on Mechanisms of Carcinogenesis

Chromosomal aberrations, sister chromatid exchange, and aneuploidy were observed in workers exposed to chromium(VI) compounds. Chromium(VI) compounds also caused genetic damage in a variety of test systems. Most caused mutations and DNA damage in bacteria; however, the poorly soluble compounds had to be dissolved in acids or alkalis to produce genetic effects. A few compounds also caused mutations in yeast and insects. Many chromium(VI) compounds caused genetic damage in cultured human and other animal cells and in experimental animals exposed *in vivo*. The compounds tested included ammonium chromate and dichromate, calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, strontium chromate, and the industrial product basic zinc chromate (zinc yellow). Among the types of genetic damage observed were gene mutations (including dominant lethal mutations), DNA damage, sister chromatid exchange, chromosomal aberrations, and cell transformation (IARC 1990).

IARC (1990) concluded that there was sufficient evidence in humans for the carcinogenicity of chromium(VI) compounds based on the combined results of epidemiological studies, cancer studies in experimental animals, and evidence that chromium(VI) ions generated at critical sites in the target cells were responsible for the carcinogenic action observed.

Properties

Elemental chromium is a transition-group metal belonging to group VIB of the periodic table and has oxidation states ranging from -2 to +6, of which the divalent (+2, II), trivalent (+3, III), and hexavalent (+6, VI) forms are the most important. Elemental chromium does not occur naturally in the environment. The divalent (chromous) state is readily oxidized to the more stable trivalent (chromic) state. Although the hexavalent state (including chromates) is more stable than the divalent state, it is rarely found in nature. Chromium(VI) compounds are strong oxidizing agents and are highly corrosive. In the environment, they generally are reduced to chromium(III) compounds. The chromium(VI) compounds most commonly encountered in industry are calcium chromate, chromium trioxide, sodium chromate and dichromate, potassium chromate and dichromate, lead chromate, strontium chromate, and zinc chromate (IARC 1990, Costa 1997). However, this listing applies to all hexavalent chromium compounds, not just to those specified above.

Calcium chromate occurs as yellow crystals or a bright-yellow powder. It is slightly soluble in water and soluble in dilute acids, and it reacts with acids and ethanol. Although calcium chromate is not flammable, toxic chromium fumes may be formed in fires, and mix-

tures with boron burn violently when ignited. Chromium trioxide (also known as chromic trioxide) occurs as dark-red or brown crystals, flakes, or granular powder and is soluble in water, ethyl alcohol, ethyl ether, sulfuric acid, and nitric acid. Contact of chromium trioxide with organic chemicals may result in violent or explosive reactions, and fires with chromium trioxide may produce irritating, corrosive, and toxic gases (ATSDR 2000, HSDB 2009). Lead chromate occurs as yellow, orange, or red crystals or a yellow or orange-yellow powder that is insoluble in water, acetic acid, and ammonia but soluble in dilute nitric acid. When heated, it emits highly toxic fumes, and it may react explosively with azo dyes. The term "lead chromate" is also used to refer to various commercial lead chromate pigments (IARC 1980, 1990, HSDB 2009). Potassium chromate occurs as yellow crystals and is soluble in water but insoluble in ethanol. Potassium dichromate occurs as red or orange-red crystals and is soluble in water but insoluble in ethanol and acetone. It poses a dangerous fire risk when in contact with organic materials or finely divided combustible materials, such as sawdust (ATSDR 2000, HSDB 2009).

Sodium chromate occurs as yellow crystals and is soluble in water and slightly soluble in methanol. Although it is not flammable, toxic chromium oxide fumes may be formed in fires with sodium chromate (ATSDR 2000, HSDB 2009). Sodium dichromate occurs as bright orange-red or red hygroscopic crystals and is soluble in water and methanol. It reacts explosively with hydrazine, acetic anhydride, boron, silicon, and other materials (IARC 1980, HSDB 2009). Strontium chromate occurs as yellow monoclinic crystals or a yellow powder. It is slightly soluble in water and soluble in dilute hydrochloric acid, nitric acid, and acetic acid. It is not flammable but reacts explosively with hydrazine (HSDB 2009). Zinc chromate occurs as lemon-yellow crystals or powder. It is insoluble in cold water and acetone, sparingly soluble in hot water, and soluble in acid and liquid ammonia. Zinc chromate reacts explosively with hydrazine. The term "zinc chromate" is also used to refer to various commercial zinc and zinc potassium chromates (IARC 1990, HSDB 2009). Physical and chemical properties of these chromium(VI) compounds are listed in the following table, along with their chemical formulas.

Use

The steel industry is the major consumer of chromium. In 2007, estimated consumption of chromium in the United States by end use was 78% in stainless and heat-resisting steel, 13.8% for other steel uses, 3.7% in superalloys, and 4.5% in other alloys and end uses (Papp 2009). Alloys of stainless steel and chromium typically contain between 11.5% and 30% chromium (ATSDR 2000). Chromium(VI) compounds are widely used as corrosion inhibitors, in the manufacture of pigments, in metal finishing and chrome plating, in stainless steel production, in leather tanning, and in wood preservatives (Costa 1997, ATSDR 2000). In 1996, about 52% of all chromium compounds used in the U.S. chemical industry were used in production of wood preservatives; the rest were used in leather tanning (13%), metals finish-

ing (13%), pigments (12%), refractories (linings for high-temperature industrial furnaces) (3%), and other uses (7%) (ATSDR 2000). The use of chromium(VI) compounds in wood preservatives increased dramatically from the late 1970s to the early 2000s; however, this use is expected to decrease because of a voluntary phase-out of all residential uses of wood treated with chromated copper arsenate (pressure-treated wood) that went into effect December 31, 2003 (Brooks 2009). Chromium(VI) compounds are also used in textile-dyeing processes, printing inks, drilling muds, pyrotechnics, water treatment, and chemical synthesis (HSDB 2009).

Calcium chromate is used primarily as a corrosion inhibitor and as a depolarizer in batteries (IARC 1973, 1990, HSDB 2009). Chromium trioxide is used primarily in chrome plating and other metal finishing (particularly in the production of automobiles and military aircraft), in production of wood preservatives, as a corrosion inhibitor, and in production of organic chemicals and catalysts. Lead chromate has been used in paints and printing inks and as a colorant in vinyl, rubber, and paper. Potassium chromate is used in production of dyes and in textile-dyeing processes. Potassium dichromate has largely been replaced by sodium dichromate in many applications; however, it is still used in photomechanical processes and production of pigments and wood preservatives. Sodium chromate is used as a corrosion inhibitor and in textile dyeing processes, inks, paints, leather tanning, wood preservatives, drilling muds, cutting oils, water treatment, and production of other chromium compounds. Sodium dichromate is the primary base material for the production of chromium compounds and is used as a corrosion inhibitor, in metal treatments, in drilling muds, and in the production of dyes, wood preservatives, synthetic organic chemicals, and catalysts. Strontium chromate is used as a corrosion inhibitor and metal conditioner, in aluminum flake coatings, as a colorant in polyvinyl chloride, in pyrotechnics, in chrome plating, and for sulfate ion control in electrochemical processes. Zinc chromates are used as corrosion inhibitors and metal conditioners and in paints, varnishes, and oil colors.

Production

The United States is one of the world's leading producers of chromium compounds. U.S. primary production levels of chromium (i.e., mine production of chromite ore) have not been reported since 1961 (USGS 2010). One surface mine was developed in the United States in the mid to late 2000s (Papp 2009, 2010), but production levels have not been reported. Other domestic sources of chromium include recycled stainless-steel scrap, industry stocks, and the Defense National Stockpile. In 2009, the U.S. chromium supply from recycled stainless-steel scrap was 160,000 metric tons (353 million pounds), down from an average of 174,000 metric tons (383 million pounds) from 2000 to 2008 (Papp 2010, USGS 2010). The supply from industry stocks was not reported for 2009; however, this source supplied an average of 10,200 metric tons (23 million pounds) from 2000 to 2008. The government stockpile releases in 2009 were 1,000 metric tons (2.2

Compound	Formula	Molec. wt.	Density (g/cm ³) ^a	Melting pt.	Dec.
Calcium chromate	CaCrO ₄	156.1	2.89	NR	NR
Chromium trioxide	CrO ₃	100.0	2.70	197°C	yes
Lead chromate	PbCrO ₄	323.2	6.12	844°C	yes
Potassium chromate	K ₂ CrO ₄	194.2	2.73	975°C	NR
Potassium dichromate	K ₂ Cr ₂ O ₇	294.2	2.68	398°C	~500°C
Sodium chromate	Na ₂ CrO ₄	162.0	2.72	792°C	NR
Sodium dichromate	Na ₂ Cr ₂ O ₇	262.0	2.52	357°C	400°C
Strontium chromate	SrCrO ₄	203.6	3.90	NR	NR
Zinc chromate	ZnCrO ₄	181.4	3.40	NR	NR

Source: HSDB 2009. ^aSource specifies the temperature at which density was determined for some but not all of the compounds. Dec. = decomposes; NR = not reported.

million pounds), down from an average of 464,000 metric tons (1 billion pounds) from 2000 to 2008. In 2009, U.S. imports of chromium were 150,000 metric tons (331 million pounds), down from an average of 455,000 from 2000 to 2008, and exports were 50,000 metric tons (110 million pounds), down from an average of 181,000 metric tons (400,000 pounds) (Papp 2010). In 2009, apparent consumption of chromium was 260,000 metric tons (573 million pounds), down from average of 538,000 metric tons (1.2 billion pounds) from 2000 to 2008.

U.S. production of calcium chromate in 1977 was at least 5,450 kg (12,000 lb); no other production data and no U.S. import or export data were found. In the late 1970s and early 1980s, annual U.S. production of chromium trioxide was around 30 million kilograms (66 million pounds). Annual production capacity was 52 million kilograms (115 million pounds) in 1988; no more recent data were found. Annual U.S. imports of chromium trioxide ranged from 200,000 kg (440,000 lb) in 1977 to 16.5 million kilograms (36.4 million pounds) in 2002; 2008 imports were 8.9 million kilograms (19.6 million pounds). U.S. exports of chromium trioxide were 4.1 million kilograms (9 million pounds) in 1977, 11.6 million kilograms (25.6 million pounds) in 2000, 8.4 million kilograms (18.5 million pounds) in 2002, and 17.4 million kilograms (38.4 million pounds) in 2008 (IARC 1990, HSDB 2009, USITC 2009).

In 1966, U.S. production of potassium chromate and dichromate combined was estimated at 2.6 million to 3.8 million kilograms (5.7 million to 8.4 million pounds). Production of potassium dichromate declined throughout the 1970s, from 3.2 million kilograms (7.1 million pounds) in 1972 to 1.0 million kilograms (2.2 million pounds) in 1978. No more recent production data for potassium chromate or dichromate were found. In the mid 1980s, combined annual U.S. imports of potassium chromate and dichromate ranged from 580,000 kg (1.3 million pounds) to 1.0 million kilograms (2.2 million pounds) (IARC 1990). U.S. imports of potassium dichromate were 189,000 kg (416,000 lb) in 2002 but only 5,000 kg (11,000 lb) in 2008, while U.S. exports decreased from 26,000 kg (57,000 lb) to 77,000 kg (170,000 lb) (USITC 2009).

The United States produced 139,000 short tons of sodium chromate and dichromate combined in 1998 and 140,700 short tons in 1999 (HSDB 2009). U.S. imports of sodium chromate and dichromate were 4.2 million kilograms (9.3 million pounds) in 1982. Imports of sodium dichromate only were 18.8 million kilograms (41.4 million pounds) in 2002 and 33 million kilograms (72.8 million pounds) in 2008. U.S. exports of sodium chromate and dichromate were 8.8 million kilograms (19.4 million pounds) in 1985 and 26.3 million kilograms (58 million pounds) in 1999. Exports of sodium dichromate only were 12.6 million kilograms (27.8 million pounds) in 2002 and 31.3 million kilograms (69 million pounds) in 2008 (HSDB 2009, USITC 2009).

The United States produced 680,000 kg (1.5 million pounds) of strontium chromate in 1970 (IARC 1990). No other production data were found. U.S. imports of strontium chromate were 300,000 kg (660,000 lb) in 1978, 250,000 kg (550,000 lb) in 1982, 180,000 kg (400,000 lb) in 1984, 390,000 kg (860,000 lb) in 1985, and 120,000 kg (265,000 lb) in 1986 and 1987 (IARC 1990, HSDB 2009). No data on U.S. exports were found. The United States produced 30.6 million kilograms (67 million pounds) of lead chromate in 1972 (HSDB 2009). In 1976 and 1977, 20 million kilograms (44 million pounds) of lead chromate were used annually to produce chrome yellow and chrome orange pigments (IARC 1990). No production data were found for zinc chromate. U.S. imports of lead and zinc chromate combined were 289,000 kg (638,000 lb) in 2000, 135,500 kg (300,000 lb) in 2002, and 8.9 million kilograms (19.6 million pounds) in 2008. U.S. exports were 287,500 kg (634,000 lb) in 2000 and 125,000 kg (275,000 lb) in

2002 (USITC 2009). In 2008, no lead or zinc chromate was imported or exported.

Exposure

Chromium, in the form of unidentified chromium compounds, occurs naturally in the earth's crust and is widely distributed in air, water, soil, and food. Chromium(III) is an essential trace element in humans. The general population is exposed to some chromium(VI) compounds, but the levels of exposure vary. Environmental exposure specifically to chromium(VI) compounds is difficult to quantify, because specific forms of chromium seldom are identified in exposure studies. Although chromium(VI) compounds in the environment may be reduced to chromium(III) compounds, hexavalent forms can persist under some conditions. The general population may be exposed to chromium(VI) compounds through inhalation of ambient air, ingestion of water, or dermal contact with products that contain chromium(VI) compounds, such as pressure-treated wood. People who live near industrial facilities that use chromium(VI) compounds or near chromium waste disposal sites have the greatest potential for exposure (ATSDR 2000).

A 1990 study reported the average concentration of chromium(VI) to be 0.0012 $\mu\text{g}/\text{m}^3$ (range = < 0.001 to 3 $\mu\text{g}/\text{m}^3$) in indoor air samples collected from residences in Hudson County, New Jersey. Other reports of exposure to chromium were not specific for chromium(VI) compounds, but provide general information on exposure to chromium and chromium compounds. Between 1977 and 1984, typical total chromium concentrations in ambient air in the United States were less than 0.01 $\mu\text{g}/\text{m}^3$ in rural areas and 0.01 to 0.03 $\mu\text{g}/\text{m}^3$ in urban areas. Average atmospheric concentrations of chromium from more than 2,100 monitoring stations ranged from 0.005 to 0.525 $\mu\text{g}/\text{m}^3$. A survey of more than 3,800 tap water samples in 1974 and 1975 found chromium concentrations ranging from 0.4 to 8.0 $\mu\text{g}/\text{L}$, with a mean of 1.8 $\mu\text{g}/\text{L}$. In surveys of U.S. surface waters, chromium concentrations in rivers ranged from less than 1 to 30 $\mu\text{g}/\text{L}$, and concentrations in lakes typically were less than 5 $\mu\text{g}/\text{L}$. Typical chromium levels in most fresh foods are low; chromium was detected in vegetables, fruits, grains, cereals, eggs, meat, and fish at concentrations of between 20 and 520 $\mu\text{g}/\text{kg}$. The mean daily dietary intake of chromium was estimated to be less than 0.2 to 0.4 μg from air, 2.0 μg from water, and 60 μg from food (ATSDR 2000).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of chromium compounds since reporting began in 1988 were lowest in 2001 (about half the average from 1988 to 2000). In 2007, 1,384 facilities released 12 million pounds of chromium, and 1,147 facilities released 51 million pounds of chromium compounds. The 100 facilities with the largest releases accounted for most of the total amounts released (TRI 2009).

Most occupational exposure to chromium(VI) compounds is through inhalation or dermal contact. Exposure to specific chromium compounds varies by industry. Chromate production workers are exposed to a variety of chromium compounds, including chromium(VI) and chromium(III) compounds. Chromate pigment workers are exposed to chromates in the pigment and to soluble chromium(VI) compounds used in pigment production. Chrome platers are exposed to soluble chromium(VI) compounds and possibly to nickel. Ferrochromium workers are exposed mainly to chromium(III) compounds and possibly to chromium(VI) compounds.

Occupational exposure to chromium generally exceeds non-occupational exposure. However, concentrations of airborne chromium in workplaces have declined significantly since the 1980s because of improved emission controls. Typical concentration ranges for airborne chromium(VI) in industries that use chromium(VI) com-

pounds are as follows: stainless-steel welding, 50 to 400 $\mu\text{g}/\text{m}^3$; chromate production, 100 to 500 $\mu\text{g}/\text{m}^3$; chrome plating, 5 to 25 $\mu\text{g}/\text{m}^3$; ferrochrome alloy production, 10 to 140 $\mu\text{g}/\text{m}^3$; and chromate pigment production, 60 to 600 $\mu\text{g}/\text{m}^3$ (IARC 1990, ATSDR 2000). In the tanning industry, hides are soaked with chromium(VI) compounds in the presence of other chemicals that reduce them to chromium(III) compounds (Costa 1997); therefore, exposure in the tanning industry is almost exclusively to soluble chromium(III) (ATSDR 2000). In a study assessing chromium exposure among stainless-steel welders and mild-steel welders, chromium levels in blood, plasma, and urine were higher among the stainless-steel welders, particularly those engaged in manual metal arc welding, which produces fumes with high concentrations of total water-soluble chromium, mainly chromium(VI) (which constituted up to 61% of total soluble chromium) (Edme *et al.* 1997).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 16,576 workers potentially were exposed to chromium (types and compounds not specified), 42,043 to potassium dichromate, and 3,519 to calcium chromate (NIOSH 1976). The National Occupational Exposure Survey (conducted 1981 to 1983) estimated that 386,142 workers, including 10,433 women, potentially were exposed to chromium; 61,073, including 19,198 women, to potassium dichromate; 32,129, including 5,565 women, to calcium chromate; and 30,784, including 8,856 women, to lead chromate (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Chromium compounds are listed as mobile source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Chromium compounds are listed as hazardous air pollutants.

Urban Air Toxics Strategy: Chromium compounds have been identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Numerous hexavalent chromium compounds are designated as hazardous substances.

Effluent Guidelines: Chromium and chromium compounds are listed as toxic pollutants.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb for chromium; = 10 lb for chromic acid, sodium chromate, ammonium chromate, potassium chromate, strontium chromate, calcium chromate, lithium chromate, potassium bichromate, ammonium bichromate, sodium bichromate; = 1,000 lb for chromic acetate, chromic sulfate.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Chromium compounds are listed substances subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Wood intended to be used in residential settings cannot be treated with chromated copper arsenate.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L for chromium.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of chromium hexavalent compounds = F006, F019, K002, K003, K004, K005, K006, K007, K008, K048, K049, K050, K051, K061, K062, K069, K086, K100; on the presence of chromium = F032, F034, F035, F037, F038, K090.

Chromium compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L for total chromium.

Food and Drug Administration (FDA)

Maximum permissible level of chromium in bottled water = 0.1 mg/L.

Specified color additives may contain chromium (as chromates) under certain restrictions.

Specified color additives may contain chromium at levels no greater than 50 ppm.

Hydrolyzed leather meal used in the feed of animals may contain chromium at levels not to exceed 2.75% of the total by weight; finished feeds may not contain more than 1% hydrolyzed leather meal by weight.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.005 mg/m³ for hexavalent chromium and compounds; = 0.1 mg/m³ where the limit of 0.005 mg/m³ has been stayed or otherwise is not in effect. Comprehensive standards have been developed for occupational exposure to hexavalent chromium in any form and in any compound.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.05 mg/m³ for water-soluble chromium(VI) compounds; = 0.01 mg/m³ for insoluble chromium(VI) compounds.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 15 mg/m³ as hexavalent chromium for chromic acid and chromates.

Recommended exposure limit (REL) (time-weighted-average workday) (10-h TWA) = 0.001 mg/m³ (as hexavalent chromium).

NIOSH considers all hexavalent chromium compounds to be potential occupational carcinogens (based on listings for chromic acid and chromates and for chromyl chloride).

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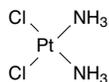
Cisplatin

CAS No. 15663-27-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as *cis*-dichlorodiammineplatinum(II)



Carcinogenicity

Cisplatin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Cisplatin caused tumors in two rodent species and at several different tissue sites. Repeated intraperitoneal injection of cisplatin caused leukemia in rats of both sexes in two studies and increased the incidence of benign lung tumors (adenoma) and number of tumors per animal in female mice. In a similar study in female mice, the incidence of benign skin tumors (papilloma) was increased when croton oil was applied to the skin as a tumor promoter (IARC 1981, 1987a).

Since cisplatin was listed in the *Fifth Annual Report on Carcinogens*, additional studies in rodents have been identified. Cisplatin administered by intraperitoneal injection caused benign lung tumors (adenoma) in female mice (Satoh *et al.* 1993), and a single intraperitoneal injection caused a dose-related increase in liver cancer (hepatocellular carcinoma) in metallothionein-I/II double-knockout mice (which lack a metal-binding protein thought to mitigate the toxicity of various metals) (Waalkes *et al.* 2006). In initiation-promotion studies in mice and rats, cisplatin acted as a tumor initiator following transplacental exposure via a single intraperitoneal injection late in gestation. In mice, transplacental exposure to cisplatin followed by dermal application of 12-*O*-tetradecanoylphorbol-13-acetate at 4 weeks of age initiated the development of benign skin tumors (papilloma). The offspring also developed thymic lymphoma and proliferative kidney lesions (renal-tubular dysplasia) in the presence or absence of the promoter (Diwan *et al.* 1993). In rats, transplacental exposure to cisplatin followed by administration of sodium barbital in the drinking water at 4 weeks of age initiated the development of benign kidney tumors (renal-cell adenoma) in males. Offspring of both sexes developed benign liver tumors (hepatocellular adenoma) in the presence or absence of the promoter (Diwan *et al.* 1995).

Cancer Studies in Humans

No epidemiological studies were available at the time cisplatin was listed in the *Fifth Annual Report on Carcinogens*. Since then, epidemiological studies have been identified, including several large case-control studies of secondary leukemia associated with cisplatin or carboplatin treatment. Excesses of leukemia were found in women treated for ovarian cancer (Kaldor *et al.* 1990, Travis *et al.* 1996) and men treated for testicular cancer (Pederson-Bjergaard *et al.* 1991, Travis *et al.* 1997, Howard *et al.* 2008). However, in most studies, the patients were also exposed to other potentially carcinogenic agents (including carboplatin and doxorubicin hydrochloride) or radiation. No studies to date have attempted to analyze the specific effects of cisplatin on the risk of secondary solid tumors. The studies on solid tumors were also limited by relatively short follow-up times. Cisplatin-based treatment without radiation was associated with a significant increase in the long-term risk of combined secondary solid

tumors among five-year survivors of testicular cancer (Van Den Belt-Dusebout *et al.* 2007).

In a number of studies, cisplatin-induced platinum-DNA adducts were observed in tissue culture (IARC 1987b) and in patients receiving cisplatin-based chemotherapy (Reed *et al.* 1993).

Properties

Cisplatin is a metallic (platinum) coordination compound with a square planar geometry that is a white or deep yellow to yellow-orange crystalline powder at room temperature. It is slightly soluble in water and soluble in dimethylprimamide and *N,N*-dimethylformamide. Cisplatin is stable under normal temperatures and pressures, but may transform slowly over time to the *trans*-isomer (IARC 1981, Akron 2009). Physical and chemical properties of cisplatin are listed in the following table.

Property	Information
Molecular weight	300.0
Density	3.74 g/m ³
Melting point	270°C (decomposes)
Log <i>K</i> _{ow}	-2.19
Water solubility	2.53 g/L at 25°C

Source: HSDB 2009.

Use

Cisplatin is a cytostatic agent used for the treatment of various malignancies, often in combination with other antineoplastic agents (IARC 1981, HSDB 2009). Since the 1970s, cisplatin has been used in the treatment of many types of cancer, including soft-tissue and osteogenic sarcoma, Kaposi's sarcoma, retinoblastoma, neuroblastoma, Wilm's tumor, gestational trophoblastic tumors, and cancer of the ovary, uterus, endometrium, cervix, prostate, urinary bladder, anus, vulva, testis, adrenal gland, lymphatic system, head and neck, skin, esophagus, thyroid gland, lung (other than small-cell cancer), breast, liver (including hepatoblastoma), stomach, and bile duct (IARC 1981, MedlinePlus 2003).

Production

Preparation of cisplatin was reported in the 1840s (IARC 1981). In 2009, cisplatin was produced by eleven manufacturers worldwide, including four in India, three in Central and South America, two in Europe, one each in China and Mexico, and none in the United States (SRI 2009). It was available from 35 suppliers, including 23 U.S. suppliers (ChemSources 2009), and seven drug products with cisplatin as the active ingredient were produced by five pharmaceutical companies (FDA 2009).

Exposure

Cisplatin is used in human medicine to treat a variety of malignancies (IARC 1981). It is available as injectable solutions at a concentration of 1 mg/mL, in 10- or 50-mg vials. The usual intravenous dose of cisplatin is 20 mg/m² of body surface per day for five days or 100 mg/m² once every four weeks. Doses as high as 40 mg/m² daily for five consecutive days have been used (Chabner *et al.* 2001). Manufacturing and health-care workers, including housekeeping personnel, potentially are exposed to cisplatin during its production, preparation, or administration or during cleanup of medical waste, including excretions of patients treated with cisplatin. Occupational exposure to chemotherapeutic drugs was demonstrated in a study which found that urine of nurses who administer these agents was mutagenic in bacteria-based assays (Falck *et al.* 1979). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 21,216

U.S. health-services workers, including 15,289 women, potentially were exposed to cisplatin (NIOSH 1990).

Environmental release of cisplatin may occur during its manufacture and through disposal of medical wastes (Zimmerman *et al.* 1981, NIOSH 2004, HSDB 2009). If released to water, cisplatin is likely to remain in solution and transform slowly to the trans form. If released to soil, it is likely to leach into the subsurface. Cisplatin has been shown to be nonbiodegradable (HSDB 2009).

Regulations

Food and Drug Administration (FDA)

Cisplatin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Coal Tars and Coal-Tar Pitches

CAS No. 8007-45-2 (Coal Tar)

No separate CAS No. is assigned to coal-tar pitches

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Coal tars and coal-tar pitches are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous studies, mostly case reports, have found that occupational exposure to coal tars or coal-tar pitches (coal-tar distillates) is associated with skin cancer, including scrotal cancer; workers in these studies have included patent-fuel (coal-briquette) workers, pitch loaders, workers in electrical trades, and optical-lens polishers (IARC 1985, 1987). A 1946 study in the United Kingdom found that patent-fuel workers were 500 times as likely as other workers to die of scrotal cancer. In addition, there have been many case reports of skin cancer among patients using therapeutic coal-tar preparations. Occupational exposure to coal tars or coal-tar pitches has also been associated with cancer at other tissue sites, including the lung, bladder, kidney, and digestive tract. Excesses of lung cancer were found in several epidemiological studies of workers exposed to coal-tar fumes in coal gasification and coke production, in studies of workers exposed to pitch fumes in aluminum production and calcium carbide production, and in a study of millwrights and welders exposed to coal-tar pitches and coal tars. The millwrights and welders also showed increased risks of digestive-tract cancer and leukemia. The risk of bladder cancer was increased in tar distillers and patent-fuel workers exposed to coal tars and coal-tar pitches and in aluminum production workers exposed to coal-tar pitches. The risk of kidney (renal-pelvis) cancer was increased in workers exposed to "petroleum or tar or pitch." Studies of roofers, who are exposed to coal-tar pitches, have found increased risks of cancer at other tissue sites in addition to skin, bladder, and lung cancer and leukemia, including cancer of the oral cavity, larynx, esophagus, and stomach; however, roofers are also exposed to other potentially carcinogenic agents, such as asphalt.

Cancer Studies in Experimental Animals

Dermal exposure to coal tars (including pharmaceutical and high-temperature coal tars) or coal-tar extracts caused skin tumors in mice and rabbits and lung cancer (but not skin tumors) in rats. Inhalation

exposure to coal tar from coke ovens caused skin tumors in mice and lung tumors in mice and rats. An extract of a coal-tar fume condensate administered by intramuscular injection caused tumors at the injection site (sarcoma) in mice. Dermal exposure to coal-tar pitches or coal-tar pitch extracts caused benign and malignant skin tumors in mice (IARC 1985, 1987).

Studies on Mechanisms of Carcinogenesis

Both coal tars and coal-tar pitches contain a number of known and potential carcinogens, including benzene, naphthalene, and other polycyclic aromatic hydrocarbons (PAHs). Coal-tar pitch extracts showed both tumor-initiating and tumor-promoting activity in mouse skin (IARC 1985, 1987).

Properties

Coal tars are by-products of the destructive distillation (carbonization) of coal to produce coke or gas. The composition and properties of a coal tar depend primarily on the temperature of the carbonization and to a lesser extent on the nature (source) of the coal used as feedstock. In general, coal tars are complex combinations of hydrocarbons, phenols, and heterocyclic oxygen, sulfur, and nitrogen compounds. Over 400 compounds have been identified in coal tars, and as many as 10,000 may actually be present. The PAH content of coal tars increases with increasing carbonization temperature. Coal tars typically are black or almost-black viscous liquids or semisolids with a characteristic naphthalene-like odor (ATSDR 2002). They are slightly soluble in water, partially soluble in acetone, carbon disulfide, chloroform, diethyl ether, ethanol, methanol, petroleum ether, and sodium hydroxide, and soluble in benzene and nitrobenzene. Low-temperature coal tars (formed at temperatures below 700°C) are black, viscous liquids that are denser than water and contain a lower percentage (40% to 50%) of aromatic compounds than high-temperature coal tars (IARC 1985). Coal tars are highly flammable and corrosive, and toxic gases may be released when they burn. Their vapors can form explosive mixtures with air (HSDB 2009).

Coal-tar pitches are shiny, dark-brown to black residues produced during the distillation of coal tars. They contain various PAHs, their methyl and polymethyl derivatives, and heteronuclear compounds (IARC 1985).

Use

Coal tars and coal-tar pitches have many uses in industry and in consumer products. Coal tars are used primarily for the production of refined chemicals and coal-tar products, such as creosote, coal-tar pitch, and crude naphthalene and anthracene oils from the distillation of crude coal tar. Coal tar has been used as a fuel in open-hearth furnaces and blast furnaces in the steel industry, as a binder and filler in surface-coating formulations, and as a modifier for epoxy-resin surface coatings. U.S. Pharmacopeia-grade coal tar is approved for use in denatured alcohol (IARC 1985). Coal-tar preparations have been used for many years to treat various skin conditions, such as eczema, psoriasis, seborrheic dermatitis, and dandruff. Both prescription and nonprescription preparations are available and include cleansing bars, creams, gels, lotions, ointments, shampoos, and other topical solutions and suspensions (DermNet NZ 2010). Coal tar is also registered as an active ingredient in pesticides with the U.S. Environmental Protection Agency (EPA 2003).

Coal-tar pitches are used primarily as the binder for aluminum-smelting electrodes (IARC 1984). They are also used in roofing materials, to impregnate and strengthen refractory brick (for lining industrial furnaces), and in surface coatings, such as pipe-coating enamels and black varnishes used as protective coatings for industrial

steelwork and as antifouling paints for boats. Hard pitch is used as a binder for foundry cores. Coke-oven pitch is used to produce pitch coke, which is used as the carbon component of electrodes, carbon brushes, and carbon and graphite articles. Distillation fractions and residues from high-temperature coal tars are used for road paving and construction and in the production of naphthalene, recovery of benzene, production of anthracene paste, briquetting of smokeless solid fuel, impregnation of electrodes and fibers, and manufacture of electrodes and graphite (IARC 1985).

Production

Coal tar was first produced in the United States in 1913, when over 1.0 billion pounds was produced as a by-product of coke production (IARC 1985). Because the majority of coal tar is produced by the steel industry, its production depends on the demand for steel. U.S. coal-tar production was 168.6 million gallons in 1986, 188.5 million gallons in 1987 (ATSDR 2002), and 1.8 billion pounds in 1994 (USITC 1995). In 2009, six U.S. suppliers of coal tar and one U.S. supplier of coal-tar pitch were identified (ChemSources 2009).

Exposure

The primary routes of potential human exposure to coal tars and coal-tar products are inhalation, ingestion, and dermal contact. The general population may be exposed to coal tar through its use in treating skin disorders. It has been estimated that nearly 2% of the United States population is affected by psoriasis, one of the conditions for which coal-tar ointments (containing 1% to 10% coal tar) are prescribed (IARC 1985). Others may be exposed through the use of coal-tar shampoos to treat dandruff or coal-tar ointments to treat eczema. The general population may also be exposed to coal tars present as environmental contaminants (ATSDR 2002).

Occupational exposure to coal tars and coal-tar pitches may occur at foundries and during coke production, coal gasification, and aluminum production. Coal gasification and iron and steel foundry workers potentially are also exposed to coal-tar pitch volatiles, including a variety of PAHs (IARC 1984). Coke ovens are the primary source of coal tar (NIOSH 1977). In 1970, the United States had 64 coking plants operating more than 13,000 coke ovens, with about 10,000 workers (NIOSH 1973). The numbers of plants and ovens remained essentially the same through 1975 but by 1998 had declined to 23 coking plants operating about 3,800 ovens (EPA 2001). In the early 1970s, an estimated 145,000 workers were directly or indirectly involved with coal-tar products (NIOSH 1977). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 1,354 workers potentially were exposed to coal-tar pitch (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 7,274 workers (including 42 women) potentially were exposed to coal tar, 19,021 workers (including 98 women) to coal-tar pitch, and 7,677 workers (including 78 women) to coal-tar-pitch volatiles (NIOSH 1990). No more recent occupational exposure surveys were found.

Workers potentially exposed to coal-tar pitches include those producing or using pavement tar, roofing tar, coal-tar pitch, coal-tar paints, coal-tar enamels, other coal-tar coatings, or refractory bricks. The concentrations of PAHs in ambient air ranged from 0 to 200 $\mu\text{g}/\text{m}^3$ near roof-tarring operations and from 0 to 3,700 $\mu\text{g}/\text{m}^3$ near pavement-tarring operations. Another study found that coal-tar pitch workers at a U.S. roofing site inhaled up to 53 μg of benzo[*a*]pyrene in seven hours (Hammond *et al.* 1976). The potential for skin exposure may be considerable; because of the heat, workers often wear little clothing, thereby exposing large portions of the body to coal tars or coal-tar pitches. In the skin oil of nine roofing workers (potentially

exposed to coal-tar pitch and bitumen), 0.000048 to 0.036 µg of PAHs were detected in a 36-cm² area of the forehead (Wolff *et al.* 1982).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of coal-tar pitches on ships and barges.

Department of Transportation (DOT)

Flammable coal-tar distillates are considered a hazardous material, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Air emissions of hazardous air pollutants from the handling of coal tar are regulated under certain source categories.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of certain coal-tar residues = K141, K142, K147, K148.

Coal-tar creosote is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Any drug products containing coal tar at levels of 0.5% to 5% must contain a label specifying the identity and concentration of the coal tar.

Any hair dye containing coal tar must display a warning label stating that the product contains an ingredient that has been determined to cause cancer in laboratory animals.

Certain dermal products containing coal tar must provide warning labels of specific precautions for that product.

The use of coal tar in several over-the-counter drugs is no longer recognized as safe and effective for the specified uses.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit = 0.2 mg/m³ for coal-tar-pitch volatiles – benzene-soluble fraction.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m³ for coal-tar-pitch volatiles as benzene-soluble aerosol.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.1 mg/m³ for coal-tar-pitch volatiles and coal-tar products – cyclohexane-extractable fraction.

Immediately dangerous to life and health (IDLH) limit = 80 mg/m³ for coal-tar-pitch volatiles.

Coal-tar-pitch volatiles are listed as potential occupational carcinogens.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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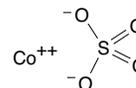
Wolff MS, Taffe B, Boesch R, Selikoff I. 1982. Detection of polycyclic aromatic hydrocarbons in skin oil obtained from roofing workers. *Chemosphere* 11(6): 595-599.

Cobalt Sulfate

CAS No. 10124-43-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Cobalt sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to cobalt sulfate by inhalation caused tumors in two rodent species and at two different tissue sites. For inhalation-exposure studies in rodents, the exposure atmospheres were generated as aerosols of cobalt sulfate heptahydrate, containing cobalt ions, sulfate ions, and water, which were partially dried before they entered the exposure chambers. (The hydrated and non-hydrated forms of a solute behave similarly when dissolved in water, both forming a solution of hydrated ions and water.) Inhalation exposure to cobalt sulfate heptahydrate caused lung cancer (alveolar/bronchiolar carcinoma) in mice of both sexes and in female rats, and it increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in male rats. It also increased the combined incidence of benign and malignant adrenal-gland tumors (pheochromocytoma) in female rats (NTP 1998).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the carcinogenicity of exposure specifically to cobalt sulfate. However, several studies evaluated the carcinogenicity of cobalt compounds as a class. Most of these studies investigated the effects of occupational exposure to hard metals (cobalt and tungsten carbide) or metallic cobalt (Lasfargues *et al.* 1994, Moulin *et al.* 1998, Wild *et al.* 2000). Although these studies consistently reported an increased risk of lung cancer among workers exposed to cobalt, the workers were also exposed to other agents (e.g., tungsten carbide) and probably were not exposed to soluble cobalt. Thus, these studies are of uncertain rele-

vance for evaluating whether exposure specifically to cobalt sulfate causes cancer. Only one study investigated the effects of exposure to cobalt salts. The initial study reported an increased risk of lung cancer among cobalt production workers, but a follow-up study of the same workers found no increased risk of cancer (Mur *et al.* 1987, Moulin *et al.* 1993). Interpretation of this finding is limited by the small number of exposed workers who developed cancer.

Studies on Mechanisms of Carcinogenesis

Cobalt sulfate did not cause mutations in most bacterial test systems studied, but it did cause genetic damage in many test systems using mammalian cells (NTP 1998). In Syrian hamster embryo cells, cobalt sulfate caused cell transformation (Kerckaert *et al.* 1996) and micronucleus formation (Gibson *et al.* 1997). In mouse fibroblasts, it caused expression of the *p53* tumor-suppressor gene (Duerksen-Hughes *et al.* 1999). In the presence of hydrogen peroxide, cobalt sulfate induced single-strand breaks and apparent intrastrand cross-links in DNA, but not the formation of 8-hydroxy-2'-deoxyguanosine adducts (Lloyd *et al.* 1997, 1998). In human lymphocytes, cobalt sulfate heptahydrate decreased the mitotic index but did not cause micronucleus formation or chromosomal aberrations (Olivero *et al.* 1995).

As a constituent of vitamin B₁₂ (cobalamin), cobalt is absorbed from the gastrointestinal tract, lungs, and skin and is distributed throughout the body. The highest concentrations are found in the liver, kidney, and heart. Cobalt is eliminated primarily in the urine, in two phases: the first phase is rapid and occurs within days, and the second may take several years (Léonard and Lauwerys 1990). The mechanism by which cobalt ions cause cancer has not been determined. It has been suggested that cobalt may replace other essential divalent metal ions (e.g., magnesium, calcium, iron, copper, or zinc), thus altering important cellular functions. Other potential mechanisms include inhibition of DNA repair and interaction with hydrogen peroxide to form reactive oxygen species that can damage DNA (Beyersmann and Hartwig 1992, Lison *et al.* 2001).

Properties

Cobalt sulfate is a cobalt compound that is a reddish to lavender crystalline solid at room temperature. It is soluble in water, sparingly soluble in methanol, and insoluble in ammonia. It is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of cobalt sulfate are listed in the following table.

Property	Information
Molecular weight	155.0
Specific gravity	3.71 at 25°C/4°C
Melting point	735°C
Water solubility	383 g/L at 25°C

Source: HSDB 2009.

Use

Cobalt sulfate is used in the electroplating and electrochemical industries; as a drier for lithographic inks, varnishes, paints, and linoleum; in storage batteries; and as a coloring agent in ceramics, enamels, glazes, and porcelain. In addition, cobalt sulfate has been used in animal feeds as a mineral supplement (Budavari *et al.* 1996, Richardson 2003) and on pastures where the forage is cobalt deficient, to provide enough cobalt for ruminants (e.g., cattle, sheep, or goats) to produce vitamin B₁₂ (EPA 1999, Washington State 1999). Past uses include addition to beer to improve the stability of the foam (NTP 1998), prevention and treatment of cobalt deficiency in ruminants, and administration to improve blood values (hematocrit, hemoglobin, and erythrocyte levels) in people with forms of anemia not responsive to other treatments (Hillman and Finch 1985, HSDB 2009).

Production

Cobalt sulfate is formed by the interaction of cobalt oxide, hydroxide, or carbonate with sulfuric acid. Production of cobalt sulfate in the United States in 1983 was estimated at 450,000 lb (NTP 1998). No more recent production data were available. Cobalt is no longer mined or refined in the United States, but negligible amounts are produced as by-products of other mining operations (USGS 2003). In 2009, cobalt sulfate was available from 18 U.S. suppliers (ChemSources 2009). In 1986, U.S. imports of cobalt sulfate were 79,700 lb (HSDB 2009). Between 1995 and 2001, annual imports ranged from about 900 metric tons to over 1,600 metric tons (2 million to 3.5 million pounds) (Shedd 2003). No information was found on U.S. exports of cobalt sulfate.

Exposure

No information was found on environmental exposure specifically to cobalt sulfate. The general population may be exposed to cobalt through inhalation of ambient air or ingestion of food or drinking water. Cobalt is an essential trace element in humans, because a cobalt atom is present in each molecule of vitamin B₁₂ (Anderson 2000). The 1999 National Health and Nutrition Examination Survey reported the geometric mean cobalt level in the urine of humans to be 0.36 µg/L of urine (95% confidence interval = 0.32 to 0.40) (CDC 2001).

No information was found on occupational exposure specifically to cobalt sulfate. However, more than a million U.S. workers potentially are exposed to cobalt or cobalt compounds (Jensen and Tüchsen 1990). Occupational exposure to cobalt occurs mainly in refining processes, in production of alloys, and in the tungsten carbide hard-metal industry (Kazantzis 1981). In addition, many workers receive limited exposure when using cobalt-containing paint driers. Occupational exposure is primarily dermal or through inhalation of cobalt metal dusts or fumes (NTP 1998, HSDB 2009). Among workers exposed to cobalt, the concentrations of cobalt in blood and urine are closely related to the average levels of cobalt in the air during a workweek (Alexandersson 1988).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Cobalt compounds are listed as hazardous air pollutants.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt compounds are listed and subject to reporting requirements.

Food and Drug Administration (FDA)

Cobaltous salts are prohibited from use in human food.

All drug products containing cobalt salts (except radioactive forms of cobalt and its salts and cobalamin and its derivatives) have been withdrawn from the market because they were found to be unsafe or not effective, and they may not be compounded.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m³ for cobalt and inorganic cobalt compounds.

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Cobalt–Tungsten Carbide: Powders and Hard Metals

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as Co/WC, WC/Co

Carcinogenicity

Cobalt–tungsten carbide powders and hard metals are *reasonably anticipated to be human carcinogens* based on limited evidence of car-

cinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Epidemiological studies provide evidence for the carcinogenicity of cobalt–tungsten carbide powders and hard metals based on (1) consistent findings of excess lung-cancer mortality among cobalt–tungsten carbide hard-metal manufacturing workers across studies, (2) higher risks among individuals with higher exposure levels, and (3) positive exposure–response relationships that cannot be explained by confounding with tobacco smoking. However, the epidemiological data are limited, because there are few studies of independent populations.

The published epidemiological literature consists of mortality studies of two independent multi-plant cohorts of cobalt–tungsten carbide hard-metal manufacturing workers, one in France (Moulin *et al.* 1998) and one in Sweden (Hogstedt and Alexandersson 1990), and cohort studies of two individual factories included in the French multi-plant cohort (Lasfargues *et al.* 1994, Wild *et al.* 2000). The French multi-plant cohort included all 10 cobalt–tungsten carbide manufacturing plants in France; in addition, a nested case-control study of lung cancer was conducted within this cohort. The nested case-control study is most informative for evaluating cancer risk, because it used a semi-quantitative exposure scale to evaluate exposure–response relationships and considered potential confounding by exposure to tobacco smoking and other known or suspected occupational carcinogens. The cohort study of the largest French factory shares these advantages; however, because the workers were included in the multi-plant study, it does not provide independent evidence for carcinogenicity. In these two studies, four metrics of exposure were evaluated: (1) exposure level, which was the highest exposure score experienced during an individual's work history (on a scale of 0 to 9), (2) duration of exposure at a level of 2 or higher, (3) unweighted cumulative dose, which assigned the same level to occasional and full-time exposure, thus favoring peak exposure, and (4) frequency-weighted cumulative dose, which weighted exposure level by the frequency of exposure, thus reducing the effect of occasional exposure. The Swedish study, although limited in size, provides supporting information for an independent population.

Excess lung-cancer mortality (of approximately 30%) was found in both multi-plant cohort studies (Hogstedt and Alexandersson 1990, Moulin *et al.* 1998); risk estimates were significantly higher among individuals with higher measures of exposure or longer time since first exposure (latency). In the nested case-control study (Moulin *et al.* 1998), lung cancer risk was significantly higher (odds ratio [OR] = 1.93, 95% CI = 1.03 to 3.62, 35 exposed cases) among workers exposed to cobalt–tungsten carbide (exposure level ≥ 2) than among workers with little or no exposure (exposure level < 2). In exposure–response analyses using workers in the lowest exposure category as the comparison group, lung-cancer risk was significantly higher (by up to fourfold) for workers in the highest categories of both measures of cumulative dose, and an elevated risk of borderline statistical significance was found for workers in the highest exposure-level category. Positive exposure–response relationships were observed for all four measures of exposure: duration ($P_{\text{trend}} = 0.03$), unweighted cumulative dose ($P_{\text{trend}} = 0.01$), frequency-weighted cumulative dose ($P_{\text{trend}} = 0.08$), and exposure level ($P_{\text{trend}} = 0.08$). Adjustment for tobacco smoking or exposure to known or suspected carcinogens did not change the results. The Swedish study had limited ability to evaluate exposure–response relationships because of small numbers of exposed workers with lung cancer. Nevertheless, the risk of lung cancer mortality was significantly increased for workers with exposure duration

of over 10 years and latency of over 20 years (standardized mortality ratio [SMR] = 2.78, 95% CI = 1.11 to 5.72, 7 exposed cases). Analyses restricted to workers with at least 10 years' exposure or at least 20 years' latency found somewhat higher SMRs for "high-exposed" than "low-exposed" workers (Hogstedt and Alexandersson 1990).

Excess risks of lung-cancer mortality were also found in studies of the two individual French factories. Wild *et al.* (2000) reported significantly elevated SMRs (by approximately twofold) for lung cancer among all male workers and among male workers ever employed in presintering workshops or with exposure levels of at least 2. The highest SMRs were observed for male workers in the highest exposure categories of all four exposure metrics (level, duration, and both measures of cumulative dose), although the trends were not statistically significant, and the risk estimates were imprecise. In the study by Lasfargues *et al.* (1994), the entire cohort had a significantly increased risk of lung cancer, and the risk was highest among workers in the highest exposure-level category. Although small, this study provides supporting evidence that the findings for the French industry-wide cohort were not due solely to the results for the large factory studied by Wild *et al.*

Both the French multi-plant cohort study (Moulin *et al.* 1988) and the larger study of an individual French factory (Wild *et al.* 2000) found higher risks of lung cancer for exposure to cobalt–tungsten carbide before sintering than after sintering (see Production). The authors stated that exposure was highest during presintering processes; however, there is no evidence of toxicological differences between presintered and sintered materials, and both materials release similar amounts of cobalt ions (see Studies on Mechanisms of Carcinogenesis).

It is unlikely that the excess risks of lung cancer found in the French studies were due to confounding by tobacco smoking or co-exposure to other known carcinogens. In the multi-plant study, the smoking-adjusted odds ratio for cobalt–tungsten carbide exposure (OR = 2.6, 95% CI = 1.16 to 5.82) was similar to the unadjusted risk (OR = 2.29, 95% CI = 1.08 to 4.88). Neither study found increased risks of smoking-related diseases, such as chronic bronchitis and emphysema, and adjustment for smoking or exposure to other occupational carcinogens did not change the findings in the exposure-response analyses (Moulin *et al.* 1988, Wild *et al.* 2000). Neither the Swedish multi-plant study (Hogstedt and Alexandersson 1990) nor the small French cohort study (Lasfargues *et al.* 1994) adjusted for smoking; however, surveys of smoking habits among a subset of workers found smoking rates similar to those in the general population. Overall, the studies are limited by the lack of quantitative exposure assessment and potential confounding; however, exposure misclassification would most likely reduce the likelihood of detecting a true effect.

Studies on Mechanisms of Carcinogenesis

The findings from epidemiological studies are supported by studies on mechanisms of carcinogenesis. Although the mechanism(s) by which by cobalt–tungsten carbide causes cancer have not been fully elucidated, it has been shown that (1) cobalt–tungsten carbide releases cobalt ions, (2) cobalt ions affect biochemical pathways related to carcinogenicity, (3) cobalt compounds are carcinogenic in experimental animals, (4) cobalt–tungsten carbide increases the production of reactive oxygen species (ROS) and causes greater cytotoxic, toxic, and genotoxic effects than does cobalt alone, (5) cobalt–tungsten carbide causes key events related to carcinogenesis, including genotoxicity, cytotoxicity, inflammation, and apoptosis (programmed cell death), and (6) the oxidative stress response resulting from increased ROS production may play a role in these key events and may also interfere with cells' ability to repair damage caused by cobalt–tungsten car-

bide. The combination of the effects from cobalt ions and the oxidative stress response from ROS production provide plausible modes of action for the carcinogenicity of cobalt–tungsten carbide.

Studies in biological fluids, *in vitro* systems, experimental animals, and humans have demonstrated that cobalt is rapidly solubilized from cobalt–tungsten carbide. Cobalt dissolution rates were similar for presintered and sintered cobalt–tungsten carbide incubated in various artificial biological fluids (Stopford *et al.* 2003). Tungsten is not rapidly solubilized from cobalt–tungsten carbide, but can be phagocytized by macrophages (Lombaert *et al.* 2004). Cobalt was also released from hard-metal dust incubated with plasma and lung tissue (Edel *et al.* 1990). In experimental animals administered cobalt–tungsten carbide by intratracheal administration, cobalt was solubilized rapidly, cleared from the lung, distributed in the body, and excreted in the urine (Lison 1996). Rats exposed intratracheally to cobalt–tungsten carbide had more cobalt in the urine than did rats administered cobalt alone, suggesting that tungsten carbide increases the bioavailability of cobalt (Lasfargues *et al.* 1992). Several biomonitoring studies detected elevated levels of cobalt in the urine, lungs, and other tissues of workers exposed to cobalt–tungsten carbide hard metals (Rizzato *et al.* 1986, Nicolaou *et al.* 1987, Gallorini *et al.* 1994, Sabbioni *et al.* 1994b, Scansetti *et al.* 1994, 1998, Linnainmaa and Kilunen 1997, Goldoni *et al.* 2004).

Soluble cobalt compounds are genotoxic and carcinogenic in experimental animals. Cobalt sulfate is listed as *reasonably anticipated to be a human carcinogen* in the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals. Specifically, inhalation exposure to cobalt sulfate in rodents caused lung tumors (adenoma or carcinoma) in mice and rats and adrenal-gland tumors (pheochromocytoma) in female rats (Bucher *et al.* 1999). Cobalt ions produce ROS, which cause oxidative DNA damage and act on a number of cancer-related molecular targets. Cobalt ions disrupt cell-signaling pathways (Murata *et al.* 1999), inhibit DNA repair (Hartwig 2000, Hartwig *et al.* 2002), regulate genes involved in the response to hypoxia (Beyersmann 2002), replace or mimic essential divalent metal ions, thus altering cellular reactions (Nackerdien *et al.* 1991, Beyersmann and Hartwig 1992, Kawanishi *et al.* 1994, Lloyd *et al.* 1998), and interfere with mechanisms involved in cell-cycle control and modulation of apoptosis (DeBoeck *et al.* 2003b,c).

Numerous *in vitro* studies (reviewed in NTP 2009) and *in vivo* studies (Huaux *et al.* 1995, Lasfargues *et al.* 1995) have shown greater cytotoxic effects (measured primarily by lactate dehydrogenase release) for cobalt–tungsten carbide than for either cobalt powder or tungsten carbide alone. The mixture's greater *in vitro* toxicity to macrophages is not fully explained by greater bioavailability of cobalt (Lison and Lauwerys 1992, 1994). Respirable samples collected at various stages of the hard-metal manufacturing process (including grinding of sintered materials) caused cytotoxicity and pathological changes in the lungs of rats after intratracheal injection (Adamis *et al.* 1997). In addition, cobalt–tungsten carbide causes a type of respiratory toxicity ("hard-metal disease") that is not observed with exposure to cobalt alone. Hard-metal disease is characterized by a giant-cell interstitial pneumonia that can develop into lung fibrosis (Lison 1996, Lison *et al.* 1996).

There is some evidence that the greater toxicity of cobalt–tungsten carbide may result from a physicochemical reaction that takes place at the interface between certain carbides and cobalt particles (Lison and Lauwerys 1992). The structural features of the two particles may help to explain the effects. Cobalt metal can reduce ambient oxygen, but only at a low rate of reaction, because of the particles' surface characteristics. Tungsten carbide is inert and does not react with oxygen

but is a good electron conductor. When cobalt and tungsten carbide particles are associated, the cobalt electrons are transferred to the carbide surface, allowing increased oxygen reduction and thus increased production of ROS. Biochemical studies on the production of ROS have shown that cobalt's capacity to generate hydroxyl radicals is greatly increased by association with tungsten carbide. Formation of the ROS results directly from the interaction of cobalt with tungsten carbide or indirectly from the cobalt ions generated from the Fenton-like reaction of the cobalt metal with the carbide (Lison and Lauwerys 1993, Lison *et al.* 1995). In oxygen-radical-generating systems, post-sintered powders sampled from final machining (grinding) of cobalt–tungsten carbide products produced higher levels of ROS than did pre-sintered samples of cobalt and tungsten carbide separately or as mixtures (Stefaniak *et al.* 2010).

Metal-induced generation of ROS in cellular test systems leads to oxidative stress as a result of increased free radicals and insufficient antioxidative defense. Protective mechanisms include cellular antioxidant systems, the stress-protein response, and the involvement of DNA excision and repair enzymes (Kasten *et al.* 1997, Shi *et al.* 2004, Lombaert *et al.* 2008). Fenoglio *et al.* (2008) studied oxidation of the antioxidant glutathione and cysteine sulfhydryl groups by cobalt–tungsten carbide dust-induced ROS and reported dust-concentration-dependent generation of thyl radicals at particle surface sites. Depletion of cellular antioxidant defenses could further exacerbate cellular oxidative damage caused by ROS generated by cobalt–tungsten carbide particles.

Regulation of gene expression, including apoptotic, stress-protein, and immune-response pathways, also can be affected by ROS. Lombaert *et al.* (2008) evaluated the effects of cobalt–tungsten carbide exposure *in vitro* on patterns of gene expression in human peripheral-blood mononucleated cells and reported statistically significant up-regulation of apoptosis and stress or defense response pathways and down-regulation of immune-response pathways.

Apoptosis has been associated with exposure to a number of known carcinogens (arsenic, cadmium, chromium, nickel, and beryllium) and possible carcinogens (cobalt and lead). Cobalt chloride has been shown to induce apoptosis through formation of ROS in both human alveolar macrophages and a rat pheochromocytoma cell line (PC12); co-administration of antioxidants suppressed ROS production and restored cell viability (Zou *et al.* 2001, Araya *et al.* 2002). Cobalt–tungsten carbide, tungsten carbide, and cobalt ions induced apoptosis in human lymphocytes; the effect of the mixture was significantly greater than that of tungsten carbide or cobalt alone (Lombaert *et al.* 2004).

Cobalt–tungsten carbide is genotoxic *in vitro* and causes mutations in the lungs of rats exposed *in vivo*. Its genotoxicity (clastogenic effects) may be caused by increased ROS production from the interaction between cobalt and tungsten carbide, from ionic cobalt, or from both. In addition, cobalt ions inhibit DNA repair, which may also contribute to cobalt–tungsten carbide's genotoxic effects. Specifically, cobalt–tungsten carbide caused DNA strand breaks in mouse 3T3 fibroblasts and human peripheral-blood lymphocytes (Anard *et al.* 1997) and micronucleus formation in human peripheral-blood lymphocytes (Van Goethem *et al.* 1997, De Boeck *et al.* 2003c). In these studies, cobalt–tungsten carbide was more genotoxic than cobalt alone. In rats exposed by intratracheal instillation, cobalt–tungsten carbide caused DNA damage and micronucleus formation in the lung (type II pneumocytes) (De Boeck *et al.* 2003a). No increase in DNA damage or micronucleus formation was observed in rat peripheral-blood lymphocytes; however, it is unclear whether circulating lymphocytes are a good reporter for monitoring genotoxic effects from inhaled particles. In humans, neither DNA damage nor micronu-

cleus formation was increased in lymphocytes of cobalt–tungsten carbide hard-metal workers, compared with unexposed workers; however, this study was limited by small sample size (De Boeck *et al.* 2000). Multiple regression analyses (Mateuca *et al.* 2005) indicated that both end points were associated with an interaction between tobacco smoking and exposure, and that micronucleus formation was associated with smoking, working in a cobalt–tungsten carbide plant, and having variant forms of genes coding for DNA repair enzymes (X-ray repair cross-complementing group 3 and 8-oxoguanine DNA glycosylase).

In addition, although the pathogenesis of hard-metal disease is not fully understood, it may involve differences in the susceptibility (genetic and/or health-related) of affected individuals to the toxic effects of increased ROS production due to cobalt–tungsten carbide exposure. Further, the mechanisms for fibrosing alveolitis and lung cancer in hard-metal workers may be related, conceivably involving oxidative damage and/or inflammatory events (IARC 2006).

Cancer Studies in Experimental Animals

No studies in experimental animals were identified that evaluated the relationship between cancer and exposure specifically to cobalt–tungsten carbide powders or hard metals.

Properties

This listing includes powders and dusts (either unsintered or sintered) containing both cobalt and tungsten carbide and hard metals containing both cobalt and tungsten carbide. Powders containing both cobalt and tungsten carbide may result from combination of these materials during manufacture of hard metals, and dusts containing both materials may result from production, finishing, or maintenance (e.g., sharpening or grinding) of cobalt–tungsten carbide hard-metal products. Cobalt–tungsten carbide hard metals are composites of tungsten carbide particles (either alone or in combination with smaller amounts of other carbides) with a metallic cobalt powder as a binder, pressed into a compact, solid form at high temperatures by a process known as “sintering.” Cobalt–tungsten carbide hard metals are commonly referred to as “cemented carbides” in the United States, but the term “sintered carbide” also may be used, and some sources refer to cobalt–tungsten carbide products simply as “tungsten carbides” (Brookes 2002).

The physical properties of cobalt–tungsten carbide hard metals vary with the relative proportions of cobalt, tungsten carbide, and other carbides, but they have common properties of extreme hardness, abrasion resistance, and toughness. Tungsten carbide is hard (able to resist cutting, abrasion, penetration, bending, and stretching) but brittle; cobalt is soft but tough (able to withstand great strain without tearing or breaking). The composition of commercial-grade cobalt–tungsten carbide hard metals can vary greatly; it generally ranges from 50% to 97% tungsten carbide (along with other metallic carbides such as titanium carbide or tantalum carbide) and from 3% to 16% cobalt, with variations in grain size and additives. The proportion of cobalt as the binding metal in the composite hard metal depends on the intended use (Azom 2002). Cobalt–tungsten carbide hard metals for various uses have Vickers hardness values (a measure of the resistance of a substance to indentation by a diamond penetrator of special profile) typically ranging from 1250 to 1900 (Brookes 1998).

The crystalline structure of cobalt–tungsten carbide includes the structures individually of cobalt, which can exist as either hexagonal or cubic crystals, and tungsten carbide, which consists primarily of W_2C , WC, and possibly other carbides (Upadhyaya 1998b). The phase diagram for the combination of cobalt and tungsten carbide is extremely complex, as tungsten can form a solid solution in co-

balt, and cobalt can form carbides with carbon; the overall relationship varies with the concentrations of the major components and the temperature.

Mixtures of cobalt and tungsten carbide are more active than the individual components in adsorption of water vapor (with respect to both the amount adsorbed and the interaction energy) and in the catalytic decomposition of hydrogen peroxide (Zanetti and Fubini 1997). Physical and chemical properties of tungsten carbide and cobalt are listed in the following table.

Property	Cobalt	Tungsten carbide
Molecular or atomic weight	58.9	195.9
Density	8.92	15.6
Melting point	1,495°C	2,785°C
Boiling point	2,927°C	6,000°C
Vapor pressure	1 Pa at 1,517°C (0.0075 mmHg)	NR

Source: HSDB 2010. NR = not reported.

Use

About 70% of cobalt–tungsten carbide hard-metal production is used for cutting tools and 30% for wear-resistant materials, primarily for tools for mining and grinding operations (Santhanam 2003). Hard-metal grades for machining are assigned International Organization for Standardization (ISO) codes beginning with “P” for machining of steel, “M” for multiple purposes, including machining of steel, nickel-based superalloys, and ductile cast iron, and “K” for cutting of gray cast iron, nonferrous metals, and nonmetallic materials.

Production

Cobalt–tungsten carbide hard metals were developed in Germany during and after World War I and marketed commercially by a German company in 1927 as Widia, which consisted of tungsten carbide with 6% cobalt as binder (Brookes 1998, Upadhyaya 1998a). Cobalt–tungsten carbide hard-metal manufacturing processes vary somewhat, but all involve production of cobalt and tungsten carbide powders, which are mixed, pressed into a compact, solid form, and sintered by heating to about 1,500°C. The manufacturing process consists of three steps: Step 1, producing the cobalt and tungsten carbide powders; Step 2, mixing, drying, pressing, presintering, shaping the presintered hard metal, and sintering; and Step 3, finishing the sintered products, which includes grinding and sharpening.

Worldwide use of cemented carbides has increased steadily over the years, from about 10 tons in 1930 to 30,000 tons per year in the early 2000s (Azom 2002). In 2004, estimated U.S. production of hard-metal products totaled 5,527 metric tons (6,080 tons) (Hsu 2004). The U.S. Geological Survey (USGS 2008a,b) estimated that 792 metric tons (873 tons) of cobalt (9.3% of total U.S. cobalt consumption) and 6,610 metric tons (7,286 tons) of tungsten (56% of total U.S. tungsten consumption) was used in the production of cemented carbides in the United States in 2007. In 2008, 127 U.S. and Canadian companies were identified that produced or supplied cobalt–tungsten carbide and materials made from cobalt–tungsten carbide (ThomasNet 2008), and the Cemented Carbide Producers Association had 22 U.S. members and partner members (CCPA 2008). In 2007, the United States imported about 1.6 million kilograms (1,800 tons) and exported about 1.3 million kilograms (1,400 tons) of tungsten carbide (USITC 2008); no data specific to U.S. imports or exports of cobalt–tungsten carbide were found.

Exposure

The major source of exposure to cobalt–tungsten carbide powders and hard metals is occupational. However, people who live in the vicinity

of hard-metal production or maintenance facilities could be exposed to cobalt–tungsten carbide hard-metal dusts. Although no exposure levels for the general population were found, some studies provided data on possible environmental contamination from the manufacture or maintenance of hard-metal products. Soil sampled from the rear of a cemented carbide tool-grinding plant contained cobalt at concentrations of up to 12,780 mg/kg (Abraham and Hunt 1995). The concentrations of tungsten and cobalt in airborne particulates in Fallon, Nevada, and four nearby towns were characterized by Sheppard *et al.* (2006), who found higher levels of tungsten (0.1 to 40.9 ng/m³) and cobalt (0.02 to 0.16 ng/m³) in Fallon than in the other towns. The authors suggested that a hard-metal facility located in Fallon could be a candidate source for airborne exposure to the metals, a suggestion that has been disputed (see NTP 2009).

Sources of occupational exposure to cobalt–tungsten carbide during the manufacture of hard metals include the processes of mixing, drying, pressing, presintering, shaping, and sintering (parts of Step 2, as described under Production) and the processes of grinding and sharpening sintered products (parts of Step 3, as described under Production). Exposure to cobalt–tungsten carbide hard metals can also occur from other miscellaneous manufacturing operations, during processing of hard-metal scrap for recycling, and during end use and maintenance of hard-metal tools. Particle size (and hence respirable fraction), morphology, and concentrations of airborne dusts and bulk dusts were found to differ among production areas (Stefaniak *et al.* 2007). For cobalt-containing particles, the minimum mass median aerodynamic diameter (MMAD) was 6 μm (for dry grinding), and the maximum MMAD was over 18 μm (for scrap reclamation and pressing operations); the MMAD for powder mixing was around 10 μm, which is generally considered the maximum diameter for respirable particles in humans. Inhalable, thoracic, and respirable particles were found in all work areas of three facilities that together carried out the cobalt–tungsten carbide manufacturing process, with the highest levels reported for the powder-mixing area (Stefaniak *et al.* 2009). Cobalt and tungsten have been detected in workers' urine, blood, hair, toenails, and bronchoalveolar lavage fluid, and through open lung and transbronchial biopsy (NTP 2009).

Step 2 processes, particularly powder-processing operations, generally are associated with the highest airborne exposures; several studies reported cobalt concentrations approaching or exceeding 5,000 μg/m³ (NTP 2009). A maximum mean cobalt air concentration of 32,740 μg/m³ (range = 44 to 438,000 μg/m³) was reported during weighing and mixing operations in a U.S. manufacturing facility (Sprince *et al.* 1984). An Italian study reported a mean tungsten air concentration of 26 μg/m³ (Sabbioni *et al.* 1994a), and a German study reported a maximum single measurement of 254 μg/m³ (Kraus *et al.* 2001). Among workers involved in Step 2 manufacturing processes, cobalt was detected in the urine (at up to 2,100 μg/L), blood or serum (at up to 32 μg/L), and hair (at up to 25.8 ppm), and tungsten was detected in urine (at up to 169 μg/L).

Cobalt air concentrations reported for Step 3 processes (including tool finishing, grinding, and reconditioning operations) have generally been lower than those for Step 2, but have exceeded 1,000 μg/m³ in some studies (NTP 2009). For Step 3 processes, a maximum mean cobalt air concentration of 1,292 μg/m³ and a maximum single measurement of 2,440 μg/m³ were reported, both for dry-grinding operations. For tungsten in air, a maximum mean concentration of 5,160 μg/m³ and a maximum single measurement of 12,800 μg/m³ were reported. Among workers involved specifically in Step 3 processes, cobalt was detected in urine (at up to 730 μg/L), blood (at up to 39 μg/L), and hair (at up to 9.11 ppm). Tungsten also was detected in urine (at up to 1,000 μg/L) and blood (at up to 60 μg/L).

A few studies reported on exposure for jobs outside of the cobalt–tungsten carbide production process. McDermott (1971) reported airborne cobalt concentrations during packing operations (10 to 250 $\mu\text{g}/\text{m}^3$), equipment cleaning (40 to 820 $\mu\text{g}/\text{m}^3$), and miscellaneous operations (10 to 6,700 $\mu\text{g}/\text{m}^3$), but the nature of these operations was not defined further. Maintenance activities (including housekeeping) were reported by Scansetti *et al.* (1985) to result in airborne cobalt concentrations exceeding 50 $\mu\text{g}/\text{m}^3$, and Kraus *et al.* (2001) reported urinary levels associated with maintenance activities ranging from 1.3 to 4.7 $\mu\text{g}/\text{L}$ for cobalt and 1.5 to 5.3 $\mu\text{g}/\text{L}$ for tungsten.

Information on exposure from the end use of hard-metal tools is limited; however, exposure appears to be minimal. Pellet *et al.* (1984, as cited in Angerer and Heinrich 1988) reported cobalt air concentrations of 180 to 193 $\mu\text{g}/\text{m}^3$ and a mean urinary cobalt concentration of 11.7 $\mu\text{g}/\text{L}$ associated with use of hard metal; however, no additional information was provided for these data. No other information was found that directly demonstrated exposure to cobalt–tungsten carbide powders and hard metals by end users of products containing the material. The Washington State Department of Labor, in a Hazard Alert issued in March 1995, stated that there was no evidence of substantial exposure to cobalt during the use of tools containing tungsten carbide or other hard metals (WSDLI 1995).

Several studies found significant correlations between cobalt concentrations in air and in workers' blood or urine (Ichikawa *et al.* 1985, Scansetti *et al.* 1985, Lison *et al.* 1994, Sabbioni *et al.* 1994b). Urinary cobalt levels for hard-metal workers have been reported to increase through the workday (Torra *et al.* 2005) and workweek (Lison *et al.* 1994, Scansetti *et al.* 1998, Torra *et al.* 2005). In one study, urinary cobalt concentrations were significantly higher ($P < 0.005$) at the end of a shift than at the beginning of the shift, with significant increases "day in and day out" during the workweek (Torra *et al.* 2005).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Water Act

Tungsten and cobalt discharge limits are imposed for numerous processes during the production of tungsten or cobalt at secondary tungsten and cobalt facilities processing tungsten or tungsten carbide scrap raw materials.

Discharge limits for tungsten are imposed for numerous processes during the production of tungsten at primary tungsten facilities.

Discharge limits for cobalt are imposed for numerous processes during the production of cobalt at primary cobalt facilities.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Cobalt and cobalt compounds are listed substances subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limits (PEL) (8-h TWA) = 0.1 mg/m^3 for cobalt metal, dust, and fume (as Co); = 5 mg/m^3 for insoluble tungsten compounds (as W).

Short-term exposure limits (STEL) = 10 mg/m^3 for insoluble tungsten compounds (as W).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.02 mg/m^3 for cobalt and inorganic cobalt compounds; = 5 mg/m^3 for tungsten metal and insoluble compounds.

Threshold limit value – short-term exposure limit (TLV-STEL) = 10 mg/m^3 for tungsten metal and insoluble compounds.

Biological exposure index (BEI) (end of shift at end of workweek) = 15 $\mu\text{g}/\text{L}$ for cobalt in urine; = 1 $\mu\text{g}/\text{L}$ for cobalt in blood.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) (10-h TWA) = 0.05 mg/m^3 for cemented tungsten carbide containing > 2% Co (as Co); = 0.05 mg/m^3 for cobalt metal dust and fume (as Co); = 5 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

Immediately dangerous to life and health (IDLH) limit = 20 mg/m^3 for cobalt metal dust and fume (as Co).

Short-term exposure limit (STEL) = 10 mg/m^3 for tungsten and insoluble tungsten compounds (as W).

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Coke-Oven Emissions

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Carcinogenicity

Coke-oven emissions are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Before 1950, numerous case reports linked employment in coke production with cancer of the skin, urinary bladder, and respiratory tract. Since then, several cohort studies conducted in the United States, the United Kingdom, Japan, and Sweden have reported an increased risk of lung cancer in humans exposed to coke-oven emissions. Smoking was accounted for in some of these studies and was not found to be a significant confounding factor. A large cohort study of 59,000 steel workers published in 1969 reported that lung-cancer risk increased

with increasing duration or intensity of exposure to coke oven fumes. Several studies of coking-plant workers reported an increased risk of kidney cancer. An excess of cancer at other tissue sites (prostate, large intestine, and pancreas) was reported in no more than one study for each site (IARC 1984, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of coke-oven emissions from studies in experimental animals. Exposure to coke-oven emissions caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Coke-oven emission samples applied weekly to the skin of mice for up to 52 weeks caused skin cancer, and these samples also showed tumor-initiating activity in initiation-promotion studies in mice. In several studies, inhalation exposure to coal-tar aerosols generated from samples collected from coke ovens caused benign and malignant lung tumors in rats and mice and skin tumors in female mice (IARC 1984).

Studies on Mechanisms of Carcinogenesis

Chemical analyses of coke-oven emissions revealed the presence of numerous known carcinogens and potentially carcinogenic chemicals, including several polycyclic aromatic hydrocarbons (PAHs), nitrosamines, coal tar, arsenic compounds, and benzene. In addition, coke-oven emissions contain several agents known to enhance the effect of chemical carcinogens, especially on the respiratory tract (IARC 1984).

Properties

Coke is produced by blending and heating bituminous coals to 1,000°C to 1,400°C in the absence of oxygen. Tars and light oils are distilled out of the coal, and gases are generated during this process. Coke-oven emissions are defined as the benzene-soluble fraction of total particulate matter generated during coke production. These emissions are complex mixtures of dusts, vapors, and gases that typically include PAHs, formaldehyde, acrolein, aliphatic aldehydes, ammonia, carbon monoxide, nitrogen oxides, phenol, cadmium, arsenic, and mercury. More than 60 organic compounds, including more than 40 PAHs, have been identified in air samples collected at coke plants. One metric ton of coal yields approximately 545 to 635 kg (1,200 to 1,400 lb) of coke, 45 to 90 kg (100 to 200 lb) of coke breeze (large coke particulates), 7 to 9 kg (15 to 20 lb) of ammonium sulfate, 27.5 to 34 L (7.3 to 9.8 gal) of coke oven gas tar, 55 to 135 L (14.5 to 35.7 gal) of ammonia liquor, and 8 to 12.5 L (2.1 to 3.3 gal) of light oil. About 20% to 35% of the initial coal charge is emitted as gases and vapors, most of which are collected in by-product coke production. Coke-oven gas includes hydrogen, methane, ethane, carbon monoxide, carbon dioxide, ethylene, propylene, butylene, acetylene, hydrogen sulfide, ammonia, oxygen, and nitrogen. Coke-oven gas tar includes pyridine, tar acids, naphthalene, creosote oil, and coal-tar pitch. Benzene, xylene, toluene, and solvent naphthas may be extracted from the light-oil fraction (IARC 1984).

Use

The primary use of coke is as a fuel reductant and support for other raw materials in iron-making blast furnaces. Coke is also used to synthesize calcium carbide and to manufacture graphite and electrodes, and coke-oven gas is used as a fuel. By-products of coke production may be refined into commodity chemicals (such as benzene, toluene, naphthalene, sulfur, and ammonium sulfate) (IARC 1984, Kaegi *et al.* 2000).

Production

Coke production in the United States increased steadily between 1880 and the early 1950s, peaking at 72 million tons in 1951. In 1976, the United States ranked second in the world in coke production, producing 52.9 million tons, or about 14.4% of world production (Kaegi *et al.* 2000). In 1990, U.S. production was 27 million tons, fourth highest worldwide. Production gradually declined from 22 million tons in 1997 to 16.8 million tons in 2002 (EIA 2003). Demand for blast-furnace coke declined because technological improvements reduced the amount of coke consumed per amount of iron produced by 10% to 25% (Kaegi *et al.* 2000). However, annual consumption from 1997 to 2002 exceeded production by 1 million to 3 million tons. Thus, for this period, U.S. imports (2.5 million to 3.8 million tons) consistently exceeded exports (0.8 to 1.3 million tons).

In 1984, it was estimated 330,000 lb to 3.5 million pounds of coke-oven emissions was produced annually in the United States (CEN 1984). Although the by-product process is designed to collect the volatile materials given off during the coking process, emissions escape because of structural defects around the doors or charging lids, improper use of engineering controls, improper work practices, and insufficient engineering controls (IARC 1984).

Exposure

The primary routes of potential human exposure to coke-oven emissions are inhalation and dermal contact. Occupational exposure may occur during the production of coke from coal or the use of coke to extract metals from ores, to synthesize calcium carbide, or to manufacture graphite and electrodes. Workers at coking plants and coal tar production plants, as well as people who live near these plants, have a high risk of possible exposure to coke-oven emissions. In 1970, the United States had 64 coking plants operating more than 13,000 coke ovens, with an estimated 10,000 coke-oven workers potentially exposed to coke-oven emissions (NIOSH 1973). The numbers of plants and ovens remained essentially the same through 1975 but by 1998 had declined to 23 coking plants operating about 3,800 ovens (EPA 2001). During the past several decades, pollution-control efforts have reduced coke-oven emissions (Costantino *et al.* 1995, Kaegi *et al.* 2000).

About 60% of total coke-oven emissions occur during charging, 30% during pushing, and 10% during quenching of the coke (Kaegi *et al.* 2000). A study reported measurements of exposure of employees to coke-oven emissions (average breathing-zone concentration) at a steel plant from 1979 to 1983, by job classification. The exposure levels depended on proximity to the oven during the coking process (Keimig *et al.* 1986). Exposure levels were highest for larry-car operator, lidman, and door-machine operator; intermediate for benchman-coke side and benchman-pusher side; and lowest for pusher operator, quencher-car operator, heater, and heater helper. Data compiled by the International Agency for Research on Cancer (IARC 1984) indicated that average concentrations of coke-oven emissions in the breathing zones of workers were lowest for pusher-machine operator (0.39 mg/m³) and highest for lidman (3.22 mg/m³), tar chaser (3.14 mg/m³), and larry-car operator (3.05 mg/m³).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.15 mg/m³ for the benzene-soluble fraction. Comprehensive standards for occupational exposure to coke-oven emissions have been developed.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.2 mg/m³ for the benzene-soluble fraction.

Listed as a potential occupational carcinogen.

References

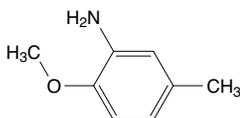
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p-Cresidine

CAS No. 120-71-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

p-Cresidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *p*-cresidine caused tumors at several different tissue sites in mice and rats. Dietary administration of *p*-cresidine caused cancer of the urinary bladder (carcinoma, including squamous- and transitional-cell carcinoma) in mice and rats of both sexes, nasal cancer (olfactory neuroblastoma) in rats of both sexes, liver cancer (hepatocellular carcinoma) in female mice, and benign liver tumors (adenoma) in male rats (NCI 1979).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to *p*-cresidine.

Properties

p-Cresidine is an aromatic amine that exists as white crystals at room temperature. It is slightly soluble in water and chloroform and soluble in ethanol, ether, benzene, and petroleum ether (HSDB 2009). Physical and chemical properties of *p*-cresidine are listed in the following table.

Property	Information
Molecular weight	137.2 ^a
Density	1.0 g/cm ³ at 20°C ^b
Melting point	52°C ^a
Boiling point	235°C ^a
Log <i>K</i> _{ow}	1.74 ^a
Water solubility	2.81 g/L at 25°C ^c
Vapor pressure	2.52 × 10 ⁻² mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

p-Cresidine is used exclusively as a synthetic chemical intermediate to produce azo dyes and pigments, such as FD&C red no. 40 and C.I. direct black 17, direct blue 67, direct blue 126, direct green 26, direct orange 34, direct orange 83, direct red 79, direct violet 51, direct yellow 41, disperse black 2, direct orange 72, and direct violet 9. The dyes made with *p*-cresidine have been produced commercially in the United States and are used in the food and textile industries (NCI 1979, IARC 1982).

Production

p-Cresidine has been produced in the United States since 1926 (IARC 1982). In 2009, *p*-cresidine was produced by one manufacturer each in the United States and Europe and two manufacturers in India (SRI 2009) and was available from 26 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports were found specifically for *p*-cresidine. Reports filed in 1986, 1990, and 1994 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *p*-cresidine totaled 1 million to 10 million pounds. The reported quantities were 500,000 lb to 1 million pounds in 1998 and 10,000 to 500,000 lb in 2002 (EPA 2004). In 2006, the quantity was less than 500,000 lb (EPA 2009).

Exposure

The routes of potential human exposure to *p*-cresidine are inhalation, ingestion, and dermal contact (HSDB 2009). *p*-Cresidine has been identified as a contaminant in FD&C red dye no. 40, which is used in gelatins, puddings, dairy products, confections, beverages, and condiments (FoodAdditives 2006, Richfield-Fratz *et al.* 1989). EPA's Toxics Release Inventory reported that in 1988, almost 13,000 lb of *p*-cresidine was released, mostly to air. From 1988 to 2002, environmental releases declined steadily except in 2000, when slightly over 12,000 lb was released to an off-site waste broker. No releases of *p*-cresidine were reported from 2002 to 2004. After 2004, releases of 260 lb (250 lb to surface water and 10 lb to air) were reported in 2005, 2006, and 2007 (TRI 2009). When released to air, *p*-cresidine is expected to exist solely as a vapor, with an estimated half-life of 2 hours. It is volatile in water, with an estimated half-life of 23 days in a river model and 169 days in a lake model. When released to soil or water, it is expected to bind to organic matter in soil, sediment,

or suspended solids, because of the reactivity of the aromatic amine group. It is not expected to hydrolyze rapidly or to bioaccumulate in aquatic organisms (HSDB 2009).

Potential occupational exposure is believed to have been limited to workers in dye-production facilities in the past (NCI 1979). No estimates were found of the number of workers potentially exposed to *p*-cresidine.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

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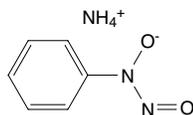
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Cupferron

CAS No. 135-20-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Cupferron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to cupferron caused tumors at several different tissue sites in mice and rats. Dietary administration of cupferron caused blood-vessel cancer (hemangiosarcoma or hemangioma) in rats and

mice of both sexes and liver cancer (hepatocellular carcinoma) in rats of both sexes and in female mice (NCI 1978). It also caused cancer of the skin of the ear (carcinoma of the auditory sebaceous gland) in female rats and mice, cancer of the forestomach (squamous-cell carcinoma) in rats of both sexes, and benign tumors of the Harderian gland (adenoma) in female mice.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to cupferron.

Properties

Cupferron is the ammonium salt of *N*-nitroso-*N*-phenylhydroxylamine and exists as a creamy-white crystalline solid at room temperature. It is soluble in water, alcohol, and ether (ChemIDplus 2009, HSDB 2009). Cupferron can produce irritating, corrosive, or toxic gases as combustion products (Akron 2009). Physical and chemical properties of cupferron are listed in the following table.

Property	Information
Molecular weight	155.2 ^a
Melting point	163°C to 164°C ^a
Log <i>K</i> _{ow}	-1.73 ^b
Water solubility	608 g/L at 25°C ^b
Vapor pressure	6.29 × 10 ⁻⁵ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Cupferron is an analytical reagent that complexes with metal ions and is used to separate and precipitate metals such as copper, iron, vanadium, and thorium. It is used to separate tin from zinc and to separate copper and iron from other metals. In analytical laboratories, cupferron is a reagent used for quantitative determination of vanadates and titanium and the colorimetric determination of aluminum (NCI 1978, HSDB 2009).

Production

In 2009, cupferron was produced by one manufacturer in East Asia and four manufacturers in India (SRI 2009) and was available from 28 suppliers, including 17 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of cupferron were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule every four years from 1986 to 2002 (except in 1994) indicated that U.S. production plus imports of cupferron totaled 10,000 to 500,000 lb (EPA 2004).

Exposure

The primary routes of potential human exposure to cupferron are ingestion and inhalation of the dust of the dry salt. Dermal contact is a secondary route of potential exposure (HSDB 2009). According to EPA's Toxics Release Inventory, the largest reported environmental releases of cupferron since 1988 were of 1,500 lb in 1989 and 1,200 lb in 1991, mostly to air. No releases were reported from 1995 to 1999, and the last year for which releases were reported was 2000, when 343 lb was released to surface water. In 2007, one industrial facility was listed as using cupferron; however, no releases were reported (TRI 2009). The potential for exposure appears to be greatest among individuals engaged in analytical or research studies involving the use of cupferron. Workers may also potentially be exposed during manufacturing processes (NCI 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 136 workers (in the Primary Metal industries), including 39 women, potentially were exposed to cupferron (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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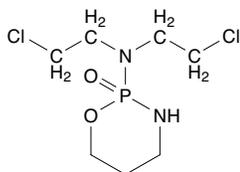
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Cyclophosphamide

CAS No. 50-18-0

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Cyclophosphamide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Several epidemiological studies consistently found excesses of urinary-bladder cancer and leukemia among people treated with cyclophosphamide for various medical conditions. A case-control study in Germany found that the risk of leukemia increased with increasing dose of cyclophosphamide (IARC 1981, 1987). More recently, a nested case-control study of non-Hodgkin's lymphoma patients reported that the risk of urinary-bladder cancer increased with increasing cumulative dose of cyclophosphamide (Travis *et al.* 1995).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of cyclophosphamide from studies in experimental animals. Exposure to cyclophosphamide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure (IARC 1981). In rats, exposure to cyclophosphamide in drinking water or by intravenous injection caused benign and malignant tumors at various tissue sites, including the urinary bladder. Cyclophosphamide administered by intraperitoneal injection to female rats caused benign and malignant mammary-gland tumors. In mice, cyclophos-

phamide administered by subcutaneous or intraperitoneal injection caused leukemia, lymphoma, and benign and malignant tumors at various sites, including the lung, liver, mammary gland, and injection site (IARC 1981, 1987).

Properties

Cyclophosphamide is an antineoplastic and immunosuppressant agent that is usually a fine white crystalline powder at room temperature. The substance liquefies and becomes an oily semisolid mass when water is removed under high vacuum. It is soluble in water, alcohol, chloroform, dioxane, and glycols, slightly soluble in benzene and carbon tetrachloride, very slightly soluble in ether and acetone, and insoluble in carbon disulfide. Cyclophosphamide is sensitive to oxidation, moisture, and light (Akron 2009). Physical and chemical properties of cyclophosphamide are listed in the following table.

Property	Information
Molecular weight	261.1 ^a
Density	1.479 g/cm ^{3b}
Melting point	49.5°C to 53°C ^a
Boiling point	336°C ^b
Log <i>K</i> _{ow}	0.63 ^a
Water solubility	40 g/L at 20°C ^a
Vapor pressure	4.45 × 10 ⁻⁵ mm Hg at 25°C ^c
Dissociation constant (p <i>K</i> _b)	9.91 ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Cyclophosphamide is used as a drug to treat cancer and other medical conditions. In chemotherapy, it may be used alone, but more frequently is used concurrently or sequentially with other anticancer drugs. Cyclophosphamide is available in the United States as 25- or 50-mg tablets, as an oral solution, or in a crystalline hydrate form for injection in strengths of 100 to 2,000 mg. It is used to treat malignant lymphoma, multiple myeloma (bone-marrow cancer), leukemia, breast and ovarian cancer, neuroblastoma (childhood nerve-cell cancer), retinoblastoma (childhood cancer of the retina), and mycosis fungoides (lymphoma of the skin) (MedlinePlus 2009, RxList 2010). Cyclophosphamide is also used as an immunosuppressive agent following organ transplants or to treat autoimmune disorders such as rheumatoid arthritis, Wegener's granulomatosis (an inflammation of the blood vessels), and nephrotic syndrome (a kidney disorder) in children (Chabner *et al.* 2001). Researchers have tested cyclophosphamide for use as an insect chemosterilant and in the chemical shearing of sheep (IARC 1975).

Production

Cyclophosphamide is not produced in the United States, and no data on U.S. imports were found. Total U.S. sales were 600 kg (1,300 lb) annually in the mid 1970s (IARC 1975); more recent data were not found. In 2009, cyclophosphamide was available from seven U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing cyclophosphamide as the active ingredient were produced by eleven U.S. pharmaceutical companies (FDA 2009).

Exposure

The general population is not expected to be exposed to cyclophosphamide, because its use is limited to medical treatment. An estimated 500,000 patients worldwide are treated with cyclophosphamide annually (Travis *et al.* 1995). Doses used in medical treatment depend on the patient and the specific disease. Cyclophosphamide may be given orally (in 25- or 50-mg tablet form) or by intravenous injection.

tion (from 100-, 200-, or 500-mg or 1- or 2-g vials) (FDA 2009). The initial treatment for cancer patients with no hematologic deficiency may be 40 to 50 mg/kg of body weight in divided intravenous doses over two to five days; other regimens are 10 to 15 mg/kg every seven to ten days or 3 to 5 mg/kg twice a week. The adult dosage for tablets typically is 1 to 5 mg/kg per day for both initial and maintenance treatment of cancer. For nonmalignant diseases, an oral dose of 2.5 to 3 mg/kg per day is administered for 60 to 90 days (RxList 2010). In 2009, 1,564 clinical trials using cyclophosphamide were in progress or recently completed (ClinicalTrials 2009).

Occupational exposure may occur from skin contact or inhalation of dust during drug formulation or packaging. Health professionals who handle cyclophosphamide, such as pharmacists, nurses, and physicians, could potentially be exposed during drug preparation, administration, or cleanup; however, exposure can be avoided through the use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981). In a cross-sectional study of hospital workers, handling of cyclophosphamide was clearly related to its detection in the urine (Evelo *et al.* 1986). Of 62 urine samples collected from 17 nurses and pharmacy technicians who prepared or administered antineoplastic drugs, including cyclophosphamide, 18 contained cyclophosphamide, at concentrations ranging from 50 ng/L (the limit of detection) to 10,030 ng/L. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 30,026 workers, including 20,745 women, potentially were exposed to cyclophosphamide (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of cyclophosphamide = U058.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Cyclophosphamide is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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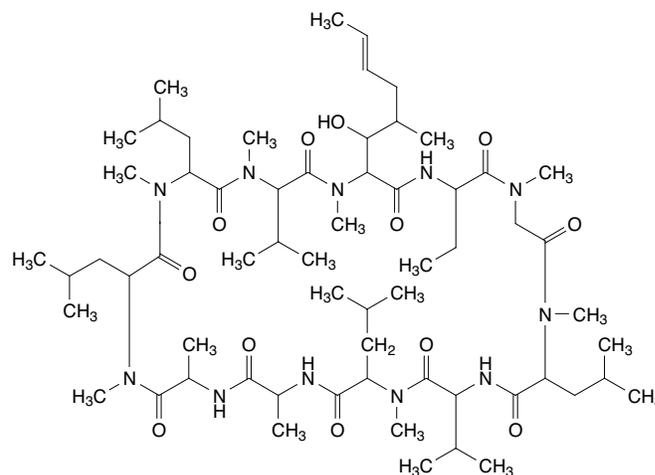
Cyclosporin A

CAS No. 59865-13-3

Known to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as ciclosporin or cyclosporine



Carcinogenicity

Cyclosporin A is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Numerous case reports describe cancer (mainly lymphoma, Kaposi's sarcoma, or skin cancer) developing in organ-transplant recipients, psoriasis patients, and rheumatoid arthritis patients treated with cyclosporin A as an immunosuppressive agent. Some of these patients were treated with cyclosporin A alone, whereas others were treated with other immunosuppressive agents in combination with cyclosporin A. The time between the start of treatment and development of tumors ranged from 1 month to 10 years. In some cases, tumors regressed after treatment with cyclosporin A was discontinued.

Several epidemiological studies (cohort studies) also indicate that cyclosporin A is carcinogenic in humans, causing tumors at an incidence of less than 5% in the patient population (IARC 1990).

Cancer Studies in Experimental Animals

Cyclosporin A administered in the diet of mice for 78 days (at doses of up to 16 ppm) or in the diet of rats for 95 to 105 weeks (at doses of up to 8 mg/kg of body weight) did not cause tumors at any tissue site. However, when male mice of a strain with a high spontaneous rate of thymus cancer (thymic lymphoma) were fed a diet containing a high dose of cyclosporin A (150 ppm) for 20 to 34 weeks, the incidence of this cancer was increased (IARC 1990). When rats with streptozotocin-induced diabetes were administered cyclosporin A in the diet at 10 mg/kg of body weight for 20 weeks, more than half developed kidney tumors; however, the incidence of these tumors in control animals was not reported (Reddi *et al.* 1991). Macaque monkeys that had received heart or heart-lung transplants (allografts) were administered cyclosporin A alone or in combination with other immunosuppressive agents, by intramuscular injection. The incidence of lymphoma (a rare neoplasm in macaques) was increased in these monkeys, but not in grafted monkeys treated with immunosuppressive regimens that did not include cyclosporin A (IARC 1990).

Studies on Mechanisms of Carcinogenesis

In tumor initiation-promotion studies, cyclosporin A increased the incidence of lymphoid tumors in male mice exposed either to radiation or *N*-methyl-*N*-nitrosourea (MNU), hepatocellular carcinoma in male rats initiated with diethylnitrosamine, and intestinal adenocarcinoma in male rats administered MNU (IARC 1990, Masuhara *et al.* 1993). Cyclosporin A also increased the incidence of cervical lymph node metastasis in hamsters exposed to dimethylbenz[*a*]anthracene (Yamada *et al.* 1992) and metastasis of tumors to the liver in male mice inoculated via the portal vein with MCA 38 colon tumor cells (Yokoyama *et al.* 1994) or colon-26 tumor cells (Suzaki *et al.* 1995). In contrast, cyclosporin A did not increase the incidence of adenoma in male mice exposed to urethane, in male rats initiated with 3-methylcholanthrene, or in rats exposed to *N*-methyl-*N*-nitro-*N*-nitrosoguanidine (IARC 1990, Bussiere *et al.* 1991).

Cyclosporin A did not cause genetic damage in a number of test systems, including gene mutation in prokaryotes, gene mutation or chromosomal aberrations in cultured mammalian cells, chromosomal aberrations or micronucleus formation in rodent bone-marrow cells, DNA repair in mouse testicular cells, or dominant lethal mutation in male mice (IARC 1990, Zwanenburg and Cordier 1994). However, cyclosporin A did cause sister chromatid exchange in human lymphocytes *in vitro* and unscheduled DNA synthesis and chromosomal aberrations in the peripheral blood lymphocytes of kidney-transplant patients treated with cyclosporin A and prednisolone (IARC 1990).

The most likely explanation for the increased incidence of tumors in patients treated with cyclosporin A is immune suppression (Ryffel 1992).

Properties

Cyclosporin A is an immunosuppressive agent that is a cyclic non-polar oligopeptide composed of 11 amino acid residues. It is a white crystalline solid at room temperature and is slightly soluble in water and saturated hydrocarbons, very soluble in acetone, diethyl ether, and methanol, and soluble in chloroform. It is sensitive to light, cold, and oxidation (IARC 1990). Physical and chemical properties of cyclosporin A are listed in the following table.

Property	Information
Molecular weight	1203 ^a
Melting point	148°C to 151°C ^a
Log <i>K</i> _{ow}	2.92 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Cyclosporin A has been used as an immunosuppressive agent since the mid 1980s. It is used extensively in the prevention and treatment of graft-versus-host reactions in bone-marrow transplantation and to prevent rejection of kidney, heart, and liver transplants. It is also used as an ophthalmic emulsion for the topical treatment of dry eye syndrome. In addition, it has been tested for use as therapy for a large variety of other diseases in which immunological factors may have a pathogenetic role, including Graves' disease, uveitis, Crohn's disease, ulcerative colitis, chronic active hepatitis, primary biliary cirrhosis, diabetes mellitus, myasthenia gravis, sarcoidosis, dermatomyositis, systemic lupus erythematosus, psoriasis, rheumatoid arthritis, and certain nephropathies (IARC 1990, Reents 1996). Cyclosporin A is used alone or in combination with azathioprine, prednisolone, prednisone, antilymphocyte globulin, actinomycin, cyclophosphamide, methylprednisolone, or phototherapy (e.g., PUVA, UVB). Cyclosporin A is administered orally, intravenously, or topically. Oral preparations may contain corn, castor, or olive oil in ethanol; intravenous preparations contain 33% alcohol and a castor-oil vehicle; and topical preparations may contain glycerin, castor oil, polysorbate 80, carbomer 1342, and sodium hydroxide. A microemulsion oral formula of cyclosporin A was approved by the U.S. Food and Drug Administration in 1995 (Reents 1996).

Production

Cyclosporin A may be biosynthesized by the fungus *Tolypocladium inflatum* or may be produced synthetically. It is manufactured commercially in Europe and East Asia (SRI 2009). In 2009, 20 U.S. suppliers of cyclosporin A were identified (Chem Sources 2009), and FDA-approved drug products containing cyclosporin A as the active ingredient were produced by 11 U.S. pharmaceutical companies (FDA 2009). No data on U.S. imports or exports of cyclosporin A were found.

Exposure

The primary routes of potential human exposure to cyclosporin A are intravenous and oral administration. Patients receiving immunosuppressive therapy for organ transplants, rheumatoid arthritis, and other diseases may be exposed to cyclosporin A. Cyclosporin A is available in oral capsules (25, 50, or 100 mg), 100-mg/mL oral solutions, 0.05% ophthalmic emulsions, and 50-mg/mL injectable vials (FDA 2009). In 2008, sales of one brand-name product with cyclosporin A as the active ingredient totaled over \$339 million, with over 2 million prescriptions filled, and sales of generic cyclosporin A totaled \$56 million (DrugTopics 2009a,b,c). A typical oral dosage of cyclosporin A is 18 mg/kg of body weight daily, beginning 12 hours before transplantation and continuing for one to two weeks, followed by reduction of the dosage to 5 to 10 mg/kg or less. Cyclosporin A may also be given intravenously at one third the oral dose. This drug often is given to transplant recipients for several months (IARC 1990). Occupational exposure potentially may occur among workers formulating or packaging the solutions and health-care professionals administering the drug.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Cyclosporin A is a prescription drug subject to specific labeling requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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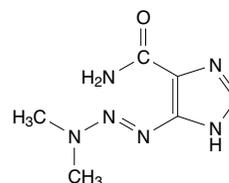
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Dacarbazine

CAS No. 4342-03-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Dacarbazine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dacarbazine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. It caused cancer of the mammary gland (adenocarcinoma), spleen (lymphosarcoma), and thymus (lymphosarcoma) in male and female rats following dietary exposure and in female rats following intraperitoneal injection. It also caused brain tumors (cerebral ependymoma) in female rats following dietary exposure. Tumors occurred as soon as 18 weeks after the start of dietary exposure. In mice, intraperitoneal injection of dacarbazine caused lung tumors in both sexes, lymphoma and blood-vessel tumors (hemangioma in the spleen) in males, and uterine tumors in females (IARC 1981).

Since dacarbazine was listed in the *Fourth Annual Report on Carcinogens*, an additional study in rodents has been identified. Prenatal exposure to dacarbazine caused tumors in rats, predominantly cancer of the peripheral nerves (malignant neurinoma) (IARC 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dacarbazine. A retrospective cohort study of Hodgkin's disease patients treated with various types of combination chemotherapy or radiotherapy evaluated records from 1,032 consecutive patients from 1965 to 1978. No secondary cases of solid tumors or acute non-lymphoblastic leukemia occurred in the subpopulation of patients treated with dacarbazine plus adriamycin, bleomycin, and vinblastine (ABVD therapy) alone or in combination with radiotherapy; however, the number of patients treated with ABVD therapy was small (Valagussa *et al.* 1980, 1982, IARC 1981, 1987).

Since dacarbazine was listed in the *Fourth Annual Report on Carcinogens*, another study of Hodgkin's disease patients has been identified, which found no increased risk of acute leukemia among patients treated with ABVD therapy alone or in combination with nonalkylating chemotherapeutic drugs (Brusamolino *et al.* 1998).

Properties

Dacarbazine is a triazene prodrug with alkylating (methylating) properties. It exists at room temperature as a white to ivory-colored microcrystalline substance. It is slightly soluble in water and is stable in neutral solutions when stored in the dark. However, it decomposes rapidly to 4-diazoimidazole-5-carboxamide when exposed to light, and it decomposes explosively at high temperatures (250°C to 255°C) (IARC 1981). Physical and chemical properties of dacarbazine are listed in the following table.

Property	Information
Molecular weight	182.2 ^a
Melting point	205°C ^a
Log <i>K</i> _{ow}	0.24 ^a
Water solubility	4.22 g/L at 25°C ^b
Vapor pressure	2.2 × 10 ⁻⁸ mm Hg at 25°C ^b
Dissociation constant (p <i>K</i> _s)	4.42 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Dacarbazine has been used as an antineoplastic agent since the early 1970s, usually in combination regimens. Dacarbazine is used in the treatment of malignant melanoma, Hodgkin's disease, neuroblastoma, osteogenic sarcoma, malignant glucagonoma, and soft-tissue sarcoma, such as leiomyosarcoma, fibrosarcoma, and rhabdomyosarcoma. It is occasionally used in therapy for other neoplastic diseases that have become resistant to alternative treatments (IARC 1981, MedlinePlus 2003).

Production

Dacarbazine is not reported to be produced in the United States. In 2009, it was produced by one manufacturer in China and one in Europe (SRI 2009) and was available from one supplier worldwide, in the United States (ChemSources 2009). Volumes of U.S. imports of dacarbazine have not been reported (IARC 1981). In 2009, nine drug products containing dacarbazine as the active ingredient were produced by five manufacturers (FDA 2009).

Exposure

Dacarbazine is available as an injectable solution in 100-, 200-, and 500-mg vials (FDA 2009). The typical initial dose is 2 to 4.5 mg/kg of body weight per day intravenously or intra-arterially for 10 days, repeated every 4 weeks, or 100 to 250 mg/m² of body surface area for 5 days, repeated every 3 weeks (IARC 1981). Health professionals and support staff, such as pharmacists, nurses, physicians, and custodians, may be exposed to dacarbazine by dermal contact, inhalation, or accidental ingestion during drug preparation, or administration or cleanup of medical waste, including excretions of patients treated with dacarbazine (Zimmerman *et al.* 1981, NIOSH 2004). Workers involved in formulation or packaging of dacarbazine drug products may also be exposed. In humans, about half of the drug is excreted unchanged in the urine (Chabner *et al.* 2001). The risks from occupational exposure can be avoided through use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981).

Regulations

Food and Drug Administration (FDA)

Dacarbazine is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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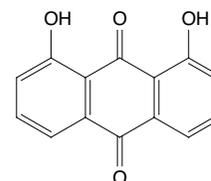
Danthron

CAS No. 117-10-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 1,8-dihydroxyanthraquinone or chrysazin



Carcinogenicity

Danthron is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to danthron caused tumors in two rodent species and at several different tissue sites. Dietary administration of danthron caused liver cancer (hepatocellular carcinoma) in male mice and benign and malignant intestinal-tract tumors (adenoma and adenocarcinoma of the colon and adenoma of the cecum) in male rats (IARC 1990).

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to danthron. One case report was identified that described the occurrence of cancer of the small intestine (leiomyosarcoma) in an

18-year-old girl with a history of prolonged exposure to danthron (Patel *et al.* 1989).

Studies on Mechanisms of Carcinogenesis

Danthron has been evaluated for its ability to promote the induction of tumors by other chemicals. When danthron was fed to male mice that also received 1,2-dimethylhydrazine as a tumor initiator, the incidence and multiplicity of colon tumors (adenoma or adenocarcinoma) and liver tumors (adenoma) were significantly increased (Sugie *et al.* 1994). However, danthron did not promote the induction of tumors when either painted on the skin of mice pretreated with 7,12-dimethylbenz[*a*]anthracene or fed to rats pretreated with 1,2-dimethylhydrazine (IARC 1990). Danthron was found to cause genetic damage in a limited number of *in vitro* test systems, including *Salmonella typhimurium*, yeast, and mammalian cell cultures (IARC 1990).

Properties

Danthron is an anthraquinone that exists at room temperature as a reddish or orange crystalline powder. It is practically insoluble in water, soluble in acetone, chloroform, diethyl ether, and ethanol, and very soluble in alkaline hydroxide solutions (IARC 1990). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of danthron are listed in the following table.

Property	Information
Molecular weight	240.2 ^a
Specific gravity	1.54 g/cm ^{3b}
Melting point	193°C ^a
Boiling point	sublimes ^b
Log <i>K</i> _{ow}	3.94 ^a
Water solubility	9 mg/L ^a
Vapor pressure	7.6 × 10 ⁻¹¹ mm Hg ^a
Vapor density relative to air	8.3 ^b

Sources: ^aChemIDplus 2009, ^bAkron 2009.

Use

Danthron has been used since the beginning of the twentieth century as a laxative (IARC 1990). In 1987, U.S. manufacturers voluntarily withdrew production of human drug products containing danthron, and in 1999, the U.S. Food and Drug Administration issued the final rule ordering the withdrawal of danthron-containing products from the U.S. market for use as laxatives (FDA 1999). However, danthron has continued to be used as a pharmaceutical in the United Kingdom (Bennett and Cresswell 2003). To a lesser extent, danthron has been used as an intermediate in the manufacture of alizarine and indanthrene dyes (Akron 2009).

Production

In the past, danthron was synthesized in Germany, India, Japan, Poland, the United Kingdom, and the United States (IARC 1990). In 2009, danthron was produced by one manufacturer in Europe and two manufacturers in China (SRI 2009) and was available from 24 suppliers, including 12 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of danthron were found. A report filed in 1986 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of danthron totaled 10,000 to 500,000 lb; no later reports were filed (EPA 2004).

Exposure

Historically, the primary route of potential human exposure to danthron has been oral administration of laxatives. Shortly before its withdrawal from the market, danthron was available from nine com-

panies in over-the-counter products. The following products were voluntarily withdrawn from the market in the United States in 1987: Altan, Antrapurol, Bancon, Benno, DanSunate D, Danthron, Diaquone, Dionone, Dorban, Dorbane, Duolax, Fructines-Vichy, Istin, Istizin, Julax, Laxanorm, Laxans, Laxanthreen, Laxenta, Laxipur, Laxipurin, Modane, Neokutin S, Pastomin, Prugol, Roydan, Scatron D, Solven, Unilax, and Zwitsalax (NTP 1999). Danthron occurs naturally in several species of plants and insects. It has been isolated from dried leaves and stems of *Xyris semifuscata* harvested in Madagascar and forms the basic structure of the aglycones of naturally occurring laxative glycosides. Danthron has been identified in larvae of the elm-leaf beetle, *Pyrrhalta luteola*; it has been suggested that the insect biosynthesizes a mixture of anthraquinones and anthrones as protection from predators (IARC 1990).

Occupational exposure to danthron potentially could have occurred among health professionals during preparation and administration of the pharmaceutical and among workers involved in its formulation and packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 357 workers (in the Health Services industry), including 187 women, potentially were exposed to danthron (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Products containing danthron as a laxative are no longer generally recognized as safe and effective and may not be marketed in the United States.

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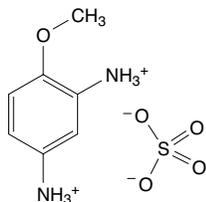
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2,4-Diaminoanisole Sulfate

CAS No. 39156-41-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

2,4-Diaminoanisole sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2,4-diaminoanisole sulfate caused thyroid-gland tumors in mice and rats, as well as tumors at several other tissue sites in rats. Dietary administration of 2,4-diaminoanisole sulfate caused thyroid-gland cancer (follicular-cell carcinoma or papillary adenocarcinoma or cystadenocarcinoma) in rats of both sexes and increased the combined incidence of benign and malignant C-cell tumors of the thyroid gland (adenoma and carcinoma) in male rats. In mice, it increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma and carcinoma) in females and benign thyroid-gland tumors (follicular-cell adenoma) in males. Dietary administration of 2,4-diaminoanisole sulfate also caused cancer of the Zymbal gland (squamous-cell carcinoma or sebaceous adenocarcinoma) in rats of both sexes. In male rats, it also caused cancer of the skin (squamous- or basal-cell carcinoma or sebaceous adenocarcinoma) and increased the combined incidence of benign and malignant tumors of the preputial gland (adenoma, papilloma, and carcinoma). In female rats, it also caused cancer of the clitoral gland (squamous- or sebaceous-cell carcinoma) and the mammary gland (adenocarcinoma); these animals also developed tumors of the pituitary gland (IARC 1978, 1982, NCI 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,4-diaminoanisole sulfate. Epidemiological studies have been conducted on professional and personal users of hair dyes; however, none of these studies specifically mentioned possible exposure to 2,4-diaminoanisole sulfate (IARC 2001).

Properties

2,4-Diaminoanisole sulfate is an aromatic amine salt that is an off-white to violet powder at room temperature (IARC 1978, 1982). It is soluble in water and ethanol and insoluble in sodium hydroxide. Physical and chemical properties of 2,4-diaminoanisole sulfate are listed in the following table.

Property	Information
Molecular weight	236.3 ^a
Melting point	66°C to 67°C ^b
Boiling point	149°C to 150°C at 5 mm Hg ^b
Log <i>K</i> _{ow}	4.19 ^c
Water solubility	1,000 g/L at 25°C ^c
Vapor pressure	1.05 × 10 ⁻¹⁴ mm Hg ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

2,4-Diaminoanisole sulfate has been used primarily as a component of oxidizing “permanent” hair- and fur-dye formulations. In 1978, about 75% of hair-dye formulations contained 2,4-diaminoanisole or its sulfate. However, a U.S. regulation requiring a warning label on all hair dyes containing 2,4-diaminoanisole or its sulfate was to become effective in April 1980, and the chemicals were voluntarily removed from products before that time (IARC 1982). 2,4-Diaminoanisole also has been used as an intermediate in the production of C.I. basic brown 2, which has been used to dye furs, acrylic fibers, cotton, wool, nylon, polyester, leather, and suede and has been an ingredient of shoe polishes (IARC 1978, 1982).

Production

Commercial production of 2,4-diaminoanisole sulfate in the United States was first reported in 1967, but no production has been reported since 1971 (IARC 1978). In 1977, annual usage of 2,4-diaminoanisole sulfate in the United States was estimated at 30,000 lb (NCI 1978). No data were found regarding U.S. production, imports, or exports of 2,4-diaminoanisole sulfate after its voluntary removal from hair dyes. In 2009, 2,4-diaminoanisole sulfate was produced by one manufacturer (in Europe) (SRI 2009) and was available from seven suppliers worldwide, including four U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to 2,4-diaminoanisole sulfate are dermal contact and inhalation. Consumers who used hair dyes containing 2,4-diaminoanisole sulfate could have been exposed. In 1973, it was estimated that 40% of U.S. women were regular users of hair dyes. Most of the dyes used were of the permanent type, and certain of these products used 2,4-diaminoanisole sulfate as a color modifier. Before its removal from consumer products, the maximum concentration of 2,4-diaminoanisole sulfate in concentrated hair-dye preparations was approximately 1.5%. Therefore, substantial exposure of the general population to 2,4-diaminoanisole sulfate was possible (NCI 1978). No releases of 2,4-diaminoanisole sulfate to the environment were reported in the U.S. Environmental Protection Agency’s Toxics Release Inventory from 1988 to 2007; however, small amounts of 2,4-diaminoanisole were released to air in 1989 (250 lb) and 1990 (26 lb) (TRI 2009). Occupational exposure could have occurred among workers at chemical- and dye-production facilities and workers using dyes containing 2,4-diaminoanisole sulfate to dye furs, textiles, and leather. Hairdressers and cosmetologists could have been exposed through the use of hair dyes containing 2,4-diaminoanisole sulfate (NCI 1978).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Food and Drug Administration (FDA)

Hair dyes containing 2,4-diaminoanisole sulfate must contain a warning statement that the product contains an ingredient that can penetrate skin and has been determined to cause cancer in laboratory animals.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) for 2,4-diaminoanisole and its salts = minimize occupational exposure (especially skin exposures).

2,4-Diaminoanisole and its salts are listed as a potential occupational carcinogens.

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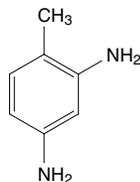
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2,4-Diaminotoluene

CAS No. 95-80-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

2,4-Diaminotoluene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

2,4-Diaminotoluene caused tumors in rats at several different tissue sites and by two different routes of exposure. Oral exposure to 2,4-diaminotoluene caused liver cancer (hepatocellular carcinoma) in male rats, and subcutaneous injection of 2,4-diaminotoluene caused cancer (sarcoma) at the injection site in rats of both sexes (IARC 1978).

Since 2,4-diaminotoluene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of 2,4-diaminotoluene caused liver cancer (hepatocellular carcinoma) in female mice and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats of both sexes. It also caused benign tumors of the subcutaneous tissue (fibroma) in male rats and increased the combined incidence of benign and malignant mammary-gland tumors (adenoma and carcinoma) in female rats. Lymphoma observed in female rats may also have been exposure-related (NCI 1979, IARC 1986). Administration of 2,4-diaminotoluene by stomach tube to male Eker rats (a strain with a high spontaneous in-

cidence of kidney tumors) caused kidney cancer (carcinoma) (Morton *et al.* 2002).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,4-diaminotoluene.

Properties

2,4-Diaminotoluene is an aromatic amine that exists at room temperature as colorless-to-brown needle-shaped crystals. It is slightly soluble in water and very soluble in alcohol, ether, and benzene. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 2,4-diaminotoluene are listed in the following table.

Property	Information
Molecular weight	122.2 ^a
Specific gravity	1.045 g/m ³ at 20°C ^b
Melting point	99°C ^a
Boiling point	292°C ^a
Log <i>K</i> _{ow}	0.337 ^a
Water solubility	7.74 g/L at 25°C ^c
Vapor pressure	5.52 × 10 ⁻⁵ mm Hg ^a
Vapor density relative to air	4.2 ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

The primary use of 2,4-diaminotoluene has been as an intermediate in the production of 2,4-toluene diisocyanate, which in turn is used to produce polyurethane (HSDB 2009). 2,4-Diaminotoluene has been used in the production of about 60 dyes, 28 of which are believed to have been produced in significant amounts in the mid 1970s. These dyes generally have been used to color silk, wool, paper, furs, and leather. Some have also been used to dye cotton fibers and other cellulosic fibers, in spirit varnishes and wood stains, as indicators in the manufacture of pigments, and as biological stains. 2,4-Diaminotoluene has been used as a developer for direct dyes, particularly to obtain black, dark blue, and brown shades, and to obtain navy blue and black colors on leather. It was also used in hair-dye formulations until this use ceased in the United States in 1971 (IARC 1978). Other applications include the preparation of impact resins, polyamides with superior wire-coating properties, antioxidants, hydraulic fluids, urethane foams, and fungicide stabilizers, and as a photographic developer (HSDB 2009).

Production

2,4-Diaminotoluene has been produced commercially in the United States since 1919. It is produced as a mixture of four diaminotoluene isomers (2,4-, 2,6-, 2,3-, and 3,4-diaminotoluene) by nitrating toluene to the dinitrotoluene isomers and reducing the mixture to the diaminotoluene isomers (IARC 1978). In 2009, 2,4-diaminotoluene was produced by nine manufacturers worldwide, including two in the United States (SRI 2009), and was available from 25 suppliers worldwide, including 18 U.S. suppliers (ChemSources 2009). U.S. imports and exports of 2,4-diaminotoluene are reported as part of a category of similar compounds, including *o*-, *m*-, and *p*-phenylenediamine, diaminotoluenes, and their derivatives and salts. Imports in this category ranged from 660,000 to 1.5 million pounds between 1989 and 2002, increasing to 4.7 million pounds in 2009. During this period, exports in this category grew from 42 million pounds in 1989 to a high of 161 million pounds in 2000 and 2003; 106.5 million pounds was exported in 2008 (USITC 2009). Reports filed in 1986, 1990, and

1994 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2,4-diaminotoluene totaled 100 million to 500 million pounds; the reported quantities fell to between 10,000 and 500,000 lb in 1998 and 2002 (EPA 2004).

Exposure

The routes of potential human exposure to 2,4-diaminotoluene are dermal contact, ingestion, surgical implantation, and inhalation (Sepai *et al.* 1995, Luu *et al.* 1998, EPA 2005, HSDB 2009, TRI 2009). 2,4-Diaminotoluene has been identified as a hydrolytic degradation product of polyester urethane foam used to cover silicone breast implants (Luu *et al.* 1998). Levels as high as 6 ng/mL were detected in plasma and urine of patients one month after surgery, and measurable levels were detected in patients up to two years after surgery (Sepai *et al.* 1995, Luu *et al.* 1998). Small amounts of 2,4-diaminotoluene have also been reported to be released from boil-in bags upon prolonged boiling (HSDB 2009).

It was estimated that 16.5 million pounds of 2,4-diaminotoluene was released during production in 1977 (HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of 2,4-diaminotoluene in most years before 2003 ranged from 500 to 4,000 lb and were mainly to air. However, over 6,000 lb was released to an off-site nonhazardous-waste landfill in 1991 and 54,000 lb to an off-site underground injection well in 1998. Since 2003, most 2,4-diaminotoluene waste has been sent to off-site hazardous and nonhazardous waste landfills. In 2007, releases totaled 18,220 lb, of which 17,000 lb was released to an off-site hazardous-waste landfill and nearly all of the rest to air (TRI 2009). When 2,4-diaminotoluene is released to air, it may photolyze and react with photochemically generated hydroxyl radicals, with an estimated half-life of 8 hours. When it is released to water, it most likely will remain in solution, where it is subject to biodegradation and photooxidation. Because it is soluble in water and has a low soil sorption partition coefficient, it will most likely leach into the subsurface when released to soil. However, it is not likely to volatilize from either water or soil (HSDB 2009).

Because 2,4-diaminotoluene can be produced from the hydrolysis of toluene diisocyanate, an intermediate in the production of polyurethane, occupational exposure to 2,4-diaminotoluene can occur through inhalation of air in polyurethane manufacturing plants (IARC 1978, EPA 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 8,511 workers (in the Textile Mill Products, Paper and Allied Products, Printing and Publishing, Chemicals and Allied Products, and Transportation Equipment industries), including 396 women, potentially were exposed to 2,4-diaminotoluene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use of 2,4-diaminotoluene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Production is subject to discharge limitations.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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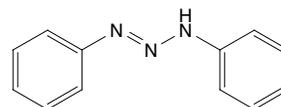
Diazoaminobenzene

CAS No. 136-35-6

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as 1,3-diphenyltriazene



Carcinogenicity

Diazoaminobenzene is *reasonably anticipated to be a human carcinogen* based on (1) evidence from studies in experimental animals and with human tissue demonstrating that diazoaminobenzene is metabolized to benzene, a known human carcinogen, and (2) evidence that diazoaminobenzene causes genetic damage. Studies in rats and mice have shown that the metabolism of diazoaminobenzene to benzene is quantitative. Benzene was listed in the First Annual Report on Carcinogens in 1980 based on human epidemiological studies dem-

onstrating that exposure to benzene causes leukemia. Benzene also causes cancer at numerous tissue sites in rodents.

Studies on Mechanisms of Carcinogenesis

Diazoaminobenzene is metabolized to benzene and to the known rodent carcinogen aniline; it also shares similar genotoxic and toxicological properties with these two carcinogens (Bordelon *et al.* 2005). In studies on the absorption, distribution, metabolism, and excretion of diazoaminobenzene orally administered to rats and mice, benzene and aniline were detected in blood, benzene was detected in exhaled breath, and metabolites of benzene and aniline were excreted in urine. Exhalation of benzene implies systemic exposure to this metabolite (Mathews and De Costa 1999; NTP 2002). Metabolites of diazoaminobenzene in the blood of rats and the urine of rats and mice included hydroquinone, muconic acid, and phenylmercapturic acid, which share benzene oxide as a common intermediate, demonstrating that the metabolic pathway of diazoaminobenzene is similar to that of benzene. In studies with human liver slices, diazoaminobenzene was reduced to benzene and aniline (Mathews and De Costa 1999). The proposed metabolic pathway for diazoaminobenzene is reductive cleavage by liver enzymes or by bacteria in the digestive tract to form benzene, aniline, and nitrogen. Benzene and aniline then are metabolized by cytochrome P450 and conjugating enzymes. Electron spin resonance studies have shown that in rats, phenyl radicals also are produced as intermediates in metabolism of diazoaminobenzene to benzene (Kadiiska *et al.* 2000).

In 16-day toxicity studies of rats and mice exposed to diazoaminobenzene (dermally, but without protection of the application site, to allow oral exposure through grooming), the symptoms observed were similar to those characteristic of benzene or aniline toxicity. Diazoaminobenzene also appeared to induce toxic effects not observed with aniline or benzene, including skin lesions at the application site (NTP 2002).

Diazoaminobenzene caused mutations in bacteria with mammalian microsomal metabolic activation (Zeiger *et al.* 1987). It also caused chromosomal aberrations in plants and micronucleus formation in the bone marrow of rodents (Ress *et al.* 2002). Benzene and aniline do not cause mutations in bacteria, but they do induce micronucleus formation in rodents. However, diazoaminobenzene orally administered to mice induced more micronuclei than did equimolar doses of benzene or a mixture of benzene and aniline. The greater genotoxicity of diazoaminobenzene than of its metabolites benzene and aniline may be due to the effects of phenyl radicals formed during its metabolism.

Cancer Studies in Experimental Animals

No studies were identified that evaluated whether exposure to diazoaminobenzene to caused cancer in experimental animals.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to diazoaminobenzene.

Properties

Diazoaminobenzene is an aromatic amine that exists as small golden-yellow crystals at room temperature. It is insoluble in water but freely soluble in benzene, ether, and hot alcohol. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of diazoaminobenzene are listed in the following table.

Property	Information
Molecular weight	197.1 ^a
Melting point	98°C ^a
Boiling point	305°C ^b
Log K_{ow}	3.99 ^c
Water solubility	0.500 g/L ^c
Vapor pressure	1.91×10^{-5} mm Hg at 25°C ^c
Vapor density relative to air	6.8 ^b
Dissociation constant (p <i>K_b</i>)	13.00 ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Diazoaminobenzene is used as a chemical intermediate, complexing agent, and polymer additive (Mathews and De Costa 1999). It has uses associated with organic synthesis and dye and insecticide manufacture (Lewis 1997), and it is an effective dopant for laser ablation (micro-machining) of polymethylmethacrylate (Bolle *et al.* 1990). Diazoaminobenzene has been identified as a low-level contaminant in the dyes D&C red no. 33, FD&C yellow no. 5 (tartrazine), and FD&C yellow no. 6; all three are permitted for use in drugs and cosmetics, and the latter two are permitted in food (FDA 2010).

Production

Diazoaminobenzene is produced by reaction of aniline with isoamyl nitrate (Smith and Ho 1990) or by diazotization of aniline dissolved in hydrochloric acid with sodium nitrite, followed by addition of sodium acetate (HSDB 2009). No information was found on levels of diazoaminobenzene production in the United States. Diazoaminobenzene was available from five U.S. suppliers in 2009 (ChemSources 2009). U.S. imports of diazoaminobenzene and *p*-aminoazobenzene-disulfonic acid (combined category) totaled 34,877 lb in 2008 (USITC 2009).

Exposure

The general population may be exposed to diazoaminobenzene through ingestion of products containing dyes or colorants or dermal exposure to such products. A 1977 study by the National Academy of Sciences reported average daily intakes of 43 mg for yellow no. 5 and 37 mg for yellow no. 6 (Feingold 2002). Thus, theoretical maximum average daily exposures to diazoaminobenzene are approximately 1.7 ng for yellow no. 5 and 1.5 ng for yellow no. 6, based on its maximum allowable levels in colorants under U.S. Food and Drug Administration regulations. Occupational exposure to diazoaminobenzene could occur from its use as a chemical intermediate and polymer additive.

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Food and Drug Administration (FDA)

The maximum level of diazoaminobenzene in color additives is 40 ppb for FD&C yellow no. 5 and no. 6 and 125 ppb for D&C red no. 33.

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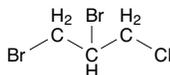
1,2-Dibromo-3-chloropropane

CAS No. 96-12-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as DBCP



Carcinogenicity

1,2-Dibromo-3-chloropropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,2-dibromo-3-chloropropane caused tumors in two rodent species and at several different tissue sites. 1,2-Dibromo-3-chloropropane administered by stomach tube caused cancer of the forestomach (squamous-cell carcinoma) in rats and mice of both sexes and mammary-gland cancer (carcinoma) in female rats (NCI 1978).

Since 1,2-dibromo-3-chloropropane was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. Inhalation exposure to 1,2-dibromo-3-chloropropane caused cancer of the nasal cavity (adenocarcinoma, carcinoma, and/or squamous-cell carcinoma) in rats and mice of both sexes. It also increased the combined incidence of benign and malignant tumors of the lung (alveolar/bronchiolar adenoma and carcinoma) in mice of both sexes and the pharynx (squamous-cell papilloma and carcinoma) in female rats, and it caused benign tumors of the tongue (squamous-cell papilloma) in rats of both sexes and the adrenal gland (cortical adenoma) in female rats (NTP 1982, IARC 1999). Exposure to 1,2-dibromo-3-chloropropane in the tank water of male and female fish (species not reported) caused cancer of the liver (hepatocellular carcinoma) and bile duct (cholangiocarcinoma) (IARC 1999).

Cancer Studies in Humans

At the time 1,2-dibromo-3-chloropropane was listed in the *Second Annual Report on Carcinogens*, no epidemiological studies had been identified that evaluated the relationship between human cancer and exposure specifically to 1,2-dibromo-3-chloropropane. Since then, relevant studies in humans have been identified. The International Agency for Research on Cancer reviewed four cohort studies of workers occupationally exposed to 1,2-dibromo-3-chloropropane and one population-based case-control study (IARC 1999). Two of the four cohort studies found an excess of lung cancer in exposed workers. The third cohort study found excesses of liver and biliary-tract cancer, and the fourth found an excess of cervical cancer. However, in some of the studies, workers were exposed to other compounds in addition to 1,2-dibromo-3-chloropropane. IARC concluded that there was inadequate evidence to evaluate the relationship between human cancer and exposure specifically to 1,2-dibromo-3-chloropropane.

Properties

1,2-Dibromo-3-chloropropane is a halogenated aliphatic hydrocarbon which at room temperature is a colorless-to-brown liquid with a pungent odor (IARC 1999). It is slightly soluble in water and miscible with most aliphatic and aromatic hydrocarbons, oils (unspecified), dichloropropane, methanol, ethanol, isopropyl alcohol, and acetone. It may burn, although it does not ignite readily and is generally considered stable (Akron 2009). Physical and chemical properties of 1,2-dibromo-3-chloropropane are listed in the following table.

Property	Information
Molecular weight	236.4
Specific gravity	2.08 at 20°C/20°C
Melting point	5°C
Boiling point	164°C at 300 mm Hg
Log K_{ow}	2.96
Water solubility	1.2 g/L at 20°C
Vapor pressure	0.58 mm Hg at 20°C
Vapor density relative to air	2.09 at 14°C

Source: HSDB 2009.

Use

1,2-Dibromo-3-chloropropane was previously registered by the U.S. Environmental Protection Agency as a soil fumigant to control nematodes for field crops, vegetables, fruits, nuts, greenhouse and nursery crops, and turf (IARC 1979, ATSDR 1992, HSDB 2009). In 1977, EPA suspended registrations for the uses of products containing the compound except for use with pineapples in Hawaii; this exception was revoked in 1985 (ATSDR 1992). Since then, 1,2-dibromo-3-chloropropane has been used in the United States only as an intermediate in organic synthesis, such as in the synthesis of the fire retardant tris(2,3-dibromopropyl)phosphate, and for research purposes (ATSDR 1992, HSDB 2009).

Production

1,2-Dibromo-3-chloropropane was first synthesized in 1833 and first produced commercially in the United States in 1955 (IARC 1979). In 1969, U.S. production was 3.9 million kilograms (8.6 million pounds). Estimates of annual production in 1974 and 1975 were 18 million to 20 million pounds (IARC 1999), and in 1977, two companies producing 1,2-dibromo-3-chloropropane were identified (ATSDR 1992). 1,2-Dibromo-3-chloropropane is no longer commercially manufactured in the United States and was not reported to be produced for sale by any manufacturing plant worldwide in 2009 (ATSDR 1992, SRI 2009). Nevertheless, 21 suppliers were identified worldwide in 2009,

including 13 U.S. suppliers (ChemSources 2009). No information on U.S. imports or exports of 1,2-dibromo-3-chloropropane was found.

Exposure

Potential routes of exposure to 1,2-dibromo-3-chloropropane include inhalation, dermal contact, and ingestion (NCI 1978). Widespread exposure of the general population or of workers to 1,2-dibromo-3-chloropropane is not likely, since registered uses of the chemical as a soil fumigant in the United States were cancelled in 1985 (ATSDR 1992). In 1974, U.S. farmers applied 9.8 million pounds of 1,2-dibromo-3-chloropropane; in 1977, 0.8 million pounds was used in California alone (HSDB 2009). Exposure of the general population to small quantities of 1,2-dibromo-3-chloropropane could still occur through ingestion or inhalation exposure to previously contaminated groundwater used as tap water and to food irrigated with contaminated groundwater. Household uses of groundwater, such as for bathing, showering, or dishwashing, might result in inhalation exposure (Clark and Snedeker 2005). However, exposure from contaminated groundwater is limited, because 1,2-dibromo-3-chloropropane was used in only a few geographical locations, and contamination is not widespread (IARC 1979, ATSDR 1992, Clark and Snedeker 2005). 1,2-Dibromo-3-chloropropane has been identified as a constituent of concern at eight hazardous-waste sites on EPA's National Priorities List, three each in California and Hawaii, and one each in Colorado and Florida (ATSDR 1992).

When released to air, 1,2-dibromo-3-chloropropane exists as a vapor and is degraded by photochemically produced hydroxyl radicals to 1,2-dibromopropanol, chlorobromopropanol, and 1-bromo-3-chloro-2-propanone, with a half-life of 37 days (HSDB 2009). Air concentrations measured while it was being applied in a vineyard by injection into the soil ranged from 3 ppb 5 feet above ground in the middle of the field to 11 ppb in the cab of the tractor pulling the injection rig. When released to surface water, 1,2-dibromo-3-chloropropane will volatilize rapidly. When released to soil, it may leach into groundwater or volatilize into the air, because it is not expected to bind strongly to soil or sediment (ATSDR 1992). Biodegradation in soil is possible, but is expected to be slow. Between 1978 and 1991, 1,2-dibromo-3-chloropropane was found in 1,829 of 20,545 groundwater-monitoring wells at concentrations of 0.001 to 8,000 µg/L. It was found in 275 drinking-water wells at concentrations of up to 7.4 µg/L.

The National Occupational Hazard Survey (conducted from 1972 and 1974) estimated that 9,682 workers were exposed to 1,2-dibromo-3-chloropropane (NIOSH 1976). No more recent estimates of the number of potentially exposed workers were found. However, its use as a soil fumigant was discontinued in 1985, and it is likely that only small amounts are used for chemical synthesis and research purposes. In 1977, exposure levels were estimated to range from less than 1 to 6 mg/m³ (100 to 600 ppb) in production and formulation plants (IARC 1979).

Regulations

Department of Transportation (DOT)

1,2-Dibromo-3-chloropropane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,2-dibromo-3-chloropropane = U066.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0002 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0002 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.001 ppm.

Comprehensive standards for occupational exposure to 1,2-dibromo-3-chloropropane have been developed.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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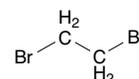
1,2-Dibromoethane

CAS No. 106-93-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as ethylene dibromide



Carcinogenicity

1,2-Dibromoethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,2-Dibromoethane caused tumors in rats and mice at several different tissue sites and by several different routes of exposure. Inhalation

exposure to 1,2-dibromoethane caused cancer of the nasal cavity (carcinoma and adenocarcinoma) and the blood vessels (hemangiosarcoma) in rats of both sexes and in female mice; benign or malignant lung tumors (alveolar/bronchiolar adenoma or carcinoma) in mice of both sexes and in female rats; and benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) in females of both species. It also caused testicular tumors (mesothelioma of the tunica vaginalis) in male rats and cancer of the subcutaneous tissue (fibrosarcoma) in female mice (NTP 1982). Dermal exposure to 1,2-dibromoethane caused lung and skin tumors in female mice (Van Duuren *et al.* 1979). Administration of technical-grade 1,2-dibromoethane by stomach tube caused cancer of the forestomach (squamous-cell carcinoma) in rats and mice of both sexes, blood-vessel cancer (hemangiosarcoma, primarily in the spleen) in male rats, benign lung tumors (alveolar-bronchiolar adenoma) in mice of both sexes, and liver cancer (hepatocellular carcinoma) in female rats (NCI 1978).

Since 1,2-dibromoethane was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. Inhalation exposure to 1,2-dibromoethane caused blood-vessel cancer (hemangiosarcoma in the spleen) and increased the combined incidence of benign and malignant adrenal-gland tumors (cortical adenoma, carcinoma, and pheochromocytoma) in rats of both sexes. It also caused mammary-gland tumors in females and skin tumors (mesenchymal tumors) in males (Wong *et al.* 1982). In mice, administration of 1,2-dibromoethane in the drinking water caused forestomach tumors (squamous-cell carcinoma) in both sexes and benign tumors of the esophagus (papilloma) in females (Van Duuren *et al.* 1985). In fish, dietary administration of 1,2-dibromoethane caused benign glandular-stomach tumors (papilloma) in both sexes (Hendricks *et al.* 1995), and administration in the tank water caused benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma), bile duct (cholangioma and cholangiocarcinoma), and gall bladder (papillary adenoma and adenocarcinoma) (Hawkins *et al.* 1998).

Cancer Studies in Humans

At the time 1,2-dibromoethane was listed in the *Second Annual Report on Carcinogens*, the data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to 1,2-dibromoethane. Since then, additional epidemiological studies have been identified. Results from three studies of occupational exposure to 1,2-dibromoethane were inconclusive, because the workers were exposed to mixtures of chemicals, and the statistical power of the studies to detect an effect was low (IARC 1999).

Properties

1,2-Dibromoethane is a volatile saturated brominated hydrocarbon that exists at room temperature as a colorless liquid with a sweet, chloroform-like odor (Akron 2009). It is only slightly soluble in water but is miscible with many organic solvents, such as diethyl ether, ethanol, acetone, and benzene. 1,2-Dibromoethane is stable in closed containers under normal conditions (Akron 2009). Physical and chemical properties of 1,2-dibromoethane are listed in the following table.

Property	Information
Molecular weight	187.9 ^a
Density	2.17 g/mL ^a
Melting point	10°C ^a
Boiling point	131°C to 132°C ^a
Log K_{ow}	1.96 ^a
Water solubility	3.91 g/L at 25°C ^b
Vapor pressure	11.2 mm Hg at 25°C ^a
Vapor density relative to air	6.5 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Historically, the primary use of 1,2-dibromoethane has been as a lead scavenger in antiknock mixtures added to gasolines (IPCS 1996). Lead scavenging agents transform the combustion products of tetraalkyl lead additives to forms that are more likely to be vaporized from engine surfaces. In 1978, 90% of the 1,2-dibromoethane produced was used for this purpose (ATSDR 1992). Annual consumption of 1,2-dibromoethane in the United States has decreased since the U.S. Environmental Protection Agency banned the use of lead in gasoline.

Another major past use of 1,2-dibromoethane was as a pesticide and an ingredient of soil and grain fumigants and for post-harvest application to various vegetable, fruit, and grain crops (NTP 1982). It also was used to kill fruit flies on citrus fruits, mangoes, and papayas after harvest and in the soil to protect grasses in environments such as golf courses (ATSDR 1992). By 1984, EPA regulations had eliminated most of the uses of 1,2-dibromoethane as a pesticide in the United States. 1,2-Dibromoethane has been used as a chemical intermediate in the manufacture of resins, gums, waxes, dyes, and pharmaceuticals and as a high-density, nonflammable solvent in a number of applications. Small amounts of 1,2-dibromoethane have been used in the manufacture of vinyl bromide, which is used as a flame retardant (ATSDR 1992, HSDB 2009).

Production

Annual U.S. production of 1,2-dibromoethane peaked at 332 million pounds in 1974, but had declined to 170 million pounds by 1982 (ATSDR 1992, HSDB 2009). In 2009, 1,2-dibromoethane was produced by six manufacturers worldwide, including one in the United States, two in India, and one each in Europe, China, and the Middle East (SRI 2009), and was available from 36 suppliers worldwide, including 18 U.S. suppliers (ChemSources 2009). Imports in the category "ethylene dibromide and fluorinated, brominated, or iodinated derivatives of acyclic hydrocarbons" have varied considerably from 1989 to 2008, from zero in 2002, 2007, and 2008 to highs of over 2 million kilograms (4.4 million pounds) in 1997 and 2000 (USITC 2009). In 1978, U.S. exports of 1,2-dibromoethane totaled 84.8 million pounds (ATSDR 1992), but from 1989 to 2008, exports declined from over 12 million kilograms (26 million pounds) to zero in 2007 and 2008 (USITC 2009). Reports filed under EPA's Toxic Substances Control Act Inventory Update Rule indicate that U.S. production plus imports of 1,2-dibromoethane declined from between 100 million and 500 million pounds in 1986 to between 1 million and 10 million pounds in 1998 and 2002 (EPA 2004).

Exposure

Potential routes of human exposure to 1,2-dibromoethane are inhalation of ambient air and ingestion of contaminated drinking water and foods. As a result of its historical use as a gasoline additive and a soil fumigant and its persistence in soil and groundwater, 1,2-dibromoethane has been detected in ambient air, soil, groundwater, and food (ATSDR 1992). According to EPA's Toxics Release Inventory, en-

Environmental releases of 1,2-dibromoethane have declined dramatically since 1988. Total releases were 99,000 lb in 1988, declining to 19,000 lb in 1994 and 10,000 lb in 2001. However, almost 48,000 lb was released in 1999. In 2007, 4,236 lb of 1,2-dibromoethane was released, over half of which was released by one facility to air (TRI 2009).

In 1980, concentrations of 1,2-dibromoethane in U.S. ambient air ranged from 0.12 to 2.826 ng/m³. Daily intake through inhalation of ambient air was estimated to range from 0 to 79 µg/kg (IPCS 1996). In addition, inhalation of 1,2-dibromoethane released to indoor air from contaminated groundwater, such as while showering, may play an important role in human exposure. Concentrations in groundwater not used for drinking water were measured at up to 90 µg/L in an irrigation well in Georgia in the early 1980s. Because 1,2-dibromoethane is readily volatilized from water, measured concentrations in surface water have not exceeded 0.2 µg/L in the United States (ATSDR 1992).

An EPA study detected 1,2-dibromoethane in slightly over 1% of public water systems tested, at mean concentration of 3.6 µg/L (EPA 2001). In California, the mean concentration in active and closed public wells was 0.006 ppb (0.006 µg/L), well below the California Department of Health Services maximum contaminant level (MCL) of 0.02 ppb (0.02 µg/L) (Kloos 1996). However, 1,2-dibromoethane was present at concentrations above the MCL in groundwater at about half of the underground storage tank sites tested (Falta *et al.* 2005). In a rural county in Kansas, the municipal water supply exceeded the U.S. EPA MCL for 1,2-dibromoethane (0.05 µg/L) on six occasions, the highest reported concentration being 0.18 µg/L (Neuberger *et al.* 2004). EPA estimated daily intake of 1,2-dibromoethane from drinking water to range from 0 to 16 µg/kg (ATSDR 1992).

Groundwater and river water from areas with known 1,2-dibromoethane contamination have been used to flood cranberry bogs for irrigation. 1,2-Dibromoethane was found at concentrations of 0.04 to 0.15 µg/kg in cranberry fruits exposed to 1,2-dibromoethane-contaminated water; however, the authors concluded that most of the contamination seemed to be associated with the water on the crop and not with the flesh of the fruit (Xia and Rice 2001). In the U.S. Food and Drug Administration's Total Diet Study, 1,2-dibromoethane was found in 1 of 40 samples of sweet pickles at a concentration of 0.013 mg/kg (13 µg/kg) (FDA 2006). In Greece, where 1,2-dibromoethane has been used as a fumigant for the wax moth that attacks honeycombs, it was found in 2 of 25 samples of honey from treated hives, at concentrations of 12 and 75 µg/kg (Tananaki *et al.* 2005). EPA estimated the maximum daily intake of 1,2-dibromoethane from food to be 0.09 µg/kg (ATSDR 1992).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 8,500 workers, including about 800 women, potentially were exposed to 1,2-dibromoethane (NIOSH 1990). Eight facilities requested that the National Institute for Occupational Safety and Health make health hazard evaluation studies of their workplaces to investigate potential exposure to 1,2-dibromoethane. 1,2-Dibromoethane was detected in the air at five workplaces (White and Lybarger 1977, Markel 1980, Okawa 1980, Arenholz 1983, Thorburn and Gunter 1983). At four workplaces, personal protective equipment was recommended, even though the air concentration in two workplaces was below the OSHA limit. In the fifth workplace, no toxic effects on workers were found, and no changes to work practices were recommended.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,2-dibromoethane on ships and barges.

Department of Transportation (DOT)

1,2-Dibromoethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 1,2-dibromoethane is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations with 1,2-dibromoethane as the active ingredient have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,2-dibromoethane = U067, K117, K118, K136.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.00005 mg/L.

Food and Drug Administration (FDA)

Action levels for 1,2-dibromoethane in food and animal feed range from 0.01 to 150 ppb.

Maximum permissible level in bottled water = 0.00005 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 20 ppm.

Ceiling concentration = 30 ppm.

Acceptable peak exposure = 50 ppm (maximum duration = 5 min).

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 0.045 ppm.

Ceiling recommended exposure limit = 0.13 ppm (15-min exposure).

Immediately dangerous to life and health (IDLH) limit = 100 ppm.

Listed as a potential occupational carcinogen.

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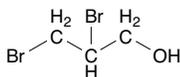
2,3-Dibromo-1-propanol

CAS No. 96-13-9

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as 2,3-dibromopropan-1-ol



Carcinogenicity

2,3-Dibromo-1-propanol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dermal exposure to 2,3-dibromo-1-propanol caused tumors at several different tissue sites in rats and mice. 2,3-Dibromo-1-propanol painted onto the skin increased the combined incidence of benign and malignant skin tumors (squamous-cell papilloma or carcinoma, basal-cell tumors, sebaceous adenoma, or keratoacanthoma) in rats and mice of both sexes. It also caused tumors (benign or malignant) at numerous other tissue sites, including the nasal mucosa, digestive tract, Zymbal gland, liver, and kidney in rats of both sexes; the mammary gland (adenocarcinoma) in female rats; the spleen (vascular tumors) and mesothelium (mesothelioma of the abdominal cavity or the tunica vaginalis of the testes) in male rats; the forestomach in mice of both sexes; and the liver and lung in male mice (NTP 1993, IARC 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,3-dibromo-1-propanol.

Studies on Mechanisms of Carcinogenesis

2,3-Dibromo-1-propanol was genotoxic in bacterial and mammalian *in vitro* test systems, including *Salmonella typhimurium*, *Escherichia coli*, V79 hamster cells, and L5178Y mouse lymphoma cells. It also caused sex-linked recessive lethal mutations and reciprocal translocations in *Drosophila melanogaster*. It caused sister chromatid exchange and chromosomal aberrations in cultured Chinese hamster ovary cells, but did not cause micronucleus formation in the bone marrow of mice administered 2,3-dibromo-1-propanol by intraperitoneal injection (IARC 2000). There is no evidence to suggest that mechanisms by which 2,3-dibromo-1-propanol causes tumors in experimental animals would not also operate in humans.

Properties

2,3-Dibromo-1-propanol is a halogenated alcohol that is a colorless to slightly yellow viscous liquid at room temperature. It is soluble in water, acetone, alcohol, ether, and benzene and is stable under normal temperatures and pressures (IARC 2000, Akron 2009). Physical and chemical properties of 2,3-dibromo-1-propanol are listed in the following table.

Property	Information
Molecular weight	217.9
Specific gravity	2.12 at 20°C/4°C
Melting point	8°C
Boiling point	219°C
Log K_{ow}	0.96
Water solubility	52 g/L at 25°C
Vapor pressure	0.09 mm Hg at 25°C
Vapor density relative to air	2.12

Source: HSDB 2009.

Use

The major use of 2,3-dibromo-1-propanol is as an intermediate in the production of flame retardants, insecticides, and pharmaceuticals, and the chemical itself has been used as a flame retardant. 2,3-Dibromo-1-propanol was used in the production of tris(2,3-

dibromopropyl) phosphate, a flame retardant used in children's clothing and other products (HSDB 2009). Tris(2,3-dibromopropyl) phosphate was banned from use in sleepwear in 1977 by the Consumer Product Safety Commission after studies showed that it caused cancer in experimental animals (NTP 1993, HSDB 2009).

Production

Production of 2,3-dibromo-1-propanol in the United States was more than 10 million pounds in 1976, but decreased drastically after the use of tris(2,3-dibromopropyl) phosphate in sleepwear was banned (NTP 1993). In 2009, 2,3-dibromo-1-propanol was produced by two manufacturers in East Asia (SRI 2009) and was available from 16 suppliers, including 9 U.S. suppliers (ChemSources 2009). Reports filed in 1986, 1990, and 1998 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2,3-dibromo-1-propanol totaled 10,000 to 500,000 lb; no inventory update reports for 2,3-dibromo-1-propanol were filed in 1994 or 2002 (EPA 2004).

Exposure

The primary routes of human exposure to 2,3-dibromo-1-propanol are inhalation and dermal contact. 2,3-Dibromo-1-propanol is a metabolite of tris(2,3-dibromopropyl) phosphate in humans (NTP 1993). Over 50 million children who wore treated sleepwear before the 1977 ban may have been exposed to 2,3-dibromo-1-propanol as a metabolite of tris(2,3-dibromopropyl) phosphate (Blum *et al.* 1978). 2,3-Dibromo-1-propanol could be released into the environment through its production and use (HSDB 2009). If released to air, 2,3-dibromo-1-propanol is expected to exist as a vapor and to be degraded by photochemically produced hydroxide radicals, with a half-life of 8 days. It is not expected to volatilize from water or soil or to adsorb to soil or sediment, and so is expected to enter groundwater if released to water or soil. Limited data suggest that it might biodegrade under aerobic conditions and that the potential for bioaccumulation is low.

Occupational exposure to 2,3-dibromo-1-propanol could occur through inhalation and dermal contact in industries where 2,3-dibromo-1-propanol is produced or is used to produce flame-retardant materials, pharmaceuticals, and insecticides (HSDB 2009). No estimates of occupational exposure to 2,3-dibromo-1-propanol were found.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 2,3-dibromo-1-propanol were identified.

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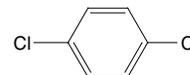
1,4-Dichlorobenzene

CAS No. 106-46-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as *p*-dichlorobenzene



Carcinogenicity

1,4-Dichlorobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,4-dichlorobenzene caused tumors at several different tissue sites in mice and rats. Administration of 1,4-dichlorobenzene by stomach tube caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice of both sexes and kidney cancer (tubular-cell adenocarcinoma) and mononuclear-cell leukemia in male rats. It also increased the combined incidence of benign and malignant adrenal-gland tumors (pheochromocytoma) in male mice (IARC 1987, NTP 1987).

Since 1,4-dichlorobenzene was listed in the *Fifth Annual Report on Carcinogens*, an additional study in mice has been identified. Inhalation exposure to 1,4-dichlorobenzene caused liver cancer (hepatocellular carcinoma and hepatoblastoma or histiocytic sarcoma) in mice of both sexes (Aiso *et al.* 2005).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dichlorobenzene. One cohort study reported five cases of leukemia associated with exposure to dichlorobenzenes (IARC 1974, 1982). The International Agency for Research on Cancer reviewed the evidence for the carcinogenicity of dichlorobenzenes in 1999, but reported no additional studies of human exposure to 1,4-dichlorobenzene (IARC 1999).

Properties

1,4-Dichlorobenzene is a chlorinated aromatic compound with a distinctive aromatic odor that is very strong at high concentrations. It is a white or colorless crystal at room temperature (Akron 2009, HSDB 2009). 1,4-Dichlorobenzene is practically insoluble in water; soluble in chloroform, carbon disulfide, benzene, and ether; and very soluble in ethanol and acetone. 1,4-Dichlorobenzene is noncorrosive, volatile, and combustible, and it is flammable when exposed to heat, flame, or oxidizers. When it is heated to decomposition, toxic gases and vapors (such as hydrochloric acid and carbon monoxide) are released (HSDB 2009). It is stable at room temperature under normal handling and storage in closed containers (Akron 2009). Physical and chemical properties of 1,4-dichlorobenzene are listed in the following table.

Property	Information
Molecular weight	147.0
Density	1.2475 g/mL at 20°C/4°C
Melting point	52.7°C
Boiling point	174°C at 760 mm Hg
Log K_{ow}	3.44
Water solubility	0.076 g/L at 25°C
Vapor pressure	1.7 mm Hg at 25°C
Vapor density relative to air	5.08

Source: HSDB 2009.

Use

1,4-Dichlorobenzene has been used primarily as a space deodorant in products such as room deodorizers and toilet deodorant blocks and as a fumigant for moth control (accounting for about 35% to 55% of the 1,4-dichlorobenzene produced) (ATSDR 1998). In 2007, it was used primarily as an intermediate in the production of polyphenylene sulfide, a plastic used in the electrical and electronics industries (52%), in the production of 1,2,4-trichlorobenzene room deodorant (22%), and for moth control (15%) (CMR 2004). Other uses of 1,4-dichlorobenzene include use as a germicide or disinfectant; a soil fumigant; an insecticide for fruit borers and ants; a chemical intermediate in the production of various dyes, pharmaceuticals, and resin-bonded abrasives; an agent to control mold and mildew growth on tobacco seeds, leather, and some fabrics; and an extreme-pressure lubricant (HSDB 2009).

Production

1,4-Dichlorobenzene was first produced commercially in the United States in 1915 (IARC 1982). In 2005, U.S. production capacity for 1,4-dichlorobenzene was reported to be 79 million pounds (CMR 2004). Demand is expected to grow by about 5% in the future because of growth in the production of polyphenylene sulfide resin, an engineering plastic that is used mainly for its insulating and dielectric properties. In 2009, 1,4-dichlorobenzene was produced by 32 manufacturers worldwide, including 1 each in the United States and Canada, 2 each in Mexico and East Asia, 4 in Europe, 9 in India, and 13 in China (SRI 2009), and it was available from 63 suppliers, including 22 U.S. suppliers (ChemSources 2009). U.S. imports of 1,4-dichlorobenzene reached a low of slightly less than 900,000 kg (2 million pounds) in 1990, increasing to almost 22 million kilograms (50 million pounds) in 2007. U.S. exports of 1,4-dichlorobenzene declined from a high of over 12 million kilograms (27 million pounds) in 2000 to slightly more than 0.5 million kilograms (1.2 million pounds) in 2005 (USITC 2009). According to reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule, U.S. production plus imports of 1,4-dichlorobenzene totaled 10 million to 50 million pounds in 1986 and 50 million to 100 million pounds between 1990 and 2002, decreasing to 10 million to 50 million pounds in 2006 (EPA 2004, 2009).

Exposure

The primary route of human exposure to 1,4-dichlorobenzene is inhalation; other potential routes are ingestion and dermal contact (ATSDR 2006). The major potential sources of consumer exposure are its uses as a deodorizer and a moth-control agent. For this reason, indoor air concentrations exceed outdoor concentrations by at least an order of magnitude. Concentrations of 1,4-dichlorobenzene in urban areas and in the vicinity of hazardous waste sites generally average less than 25.2 $\mu\text{g}/\text{m}^3$, but indoor air concentrations may be one to three orders of magnitude higher where it is used as a space deodorizer or moth repellent. 1,4-Dichlorobenzene has been detected

in meat and eggs from exposed animals and in fish from contaminated waters (IARC 1982). In the U.S. Food and Drug Administration's Total Diet Study, the concentrations measured in food and water were generally low, and exposure was less than that from air (ATSDR 2006). 1,4-Dichlorobenzene was detected 102 times in 33 different food items, at concentrations ranging from 0.002 to 0.29 ppm (in popcorn popped in oil) (FDA 2006). It has also been identified in samples of pig back fat at a concentration of 502 ng/g (Rius *et al.* 2005). Concentrations of 1,4-dichlorobenzene measured in fresh vegetables in the United Kingdom ranged from 0.027 $\mu\text{g}/\text{kg}$ of fresh weight in potatoes to 0.464 $\mu\text{g}/\text{kg}$ in peas (Wang and Jones 1994).

In 1988, EPA's Toxics Release Inventory reported environmental releases of 1.9 million pounds of 1,4-dichlorobenzene, mostly (> 99%) to air. Releases have since declined steadily; in 2007, 11 facilities released a total of 79,317 lb, mostly to air (TRI 2009). When released to water, 1,4-dichlorobenzene volatilizes rapidly; concentrations measured in surface water are generally low (median concentration < 1 ppb) (ATSDR 2006). However, concentrations as high as 400 ppb were measured in 2006 in canal water in a rural settlement in Matamoros, Tamaulipas, Mexico, along the U.S. border (Owens and Niemeyer 2006). 1,4-Dichlorobenzene was also measured in sediments from Bayou d'Inde, a tributary of the Calcasieu River near Lake Charles, Louisiana, at a concentration of 9.5 mg/kg in the solid portion and 67.1 $\mu\text{g}/\text{L}$ in the interstitial water (Prytula and Pavlostathis 1996). Measured concentrations for river environments in Canada were 0.6 to 130 ng/L in water, 520 to 34,000 ng/g of dry weight in sediment, and 920 ng/m³ in the atmosphere (Warren *et al.* 2007). In sampling of groundwater in the Edwards Aquifer, in Texas, only 3 of 27 wells had concentrations above the detection limit of 4 ng/L (Buszka *et al.* 1995). 1,4-Dichlorobenzene was also identified in municipal solid waste in Huntsville, Alabama, at a concentration of 5.8 $\mu\text{g}/\text{kg}$ (Leahy *et al.* 2004).

Occupational exposure to 1,4-dichlorobenzene occurs during its manufacture, its conversion to polyphenylene sulfide, and its other industrial uses. Concentrations of up to 4,350 mg/m³ have been measured in the air for various factory operations. In 1980, EPA reported that about 1 million workers in the United States were exposed to 1,4-dichlorobenzene, primarily by inhalation, whereas an industry survey from the same year reported that fewer than 1,000 workers were exposed during production, captive use, and shipment of 1,4-dichlorobenzene from producers (NTP 1987). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 33,978 workers, including 9,412 women, potentially were exposed to 1,4-dichlorobenzene (NIOSH 1990).

Regulations

Department of Transportation (DOT)

1,4-Dichlorobenzene is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 1,4-dichlorobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 63 $\mu\text{g}/\text{L}$; based on fish or shellfish consumption only = 190 $\mu\text{g}/\text{L}$.

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 7.5 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,4-dichlorobenzene = U072, K149, K150.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.075 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.075 mg/L.

Polyphenylene sulfide resins produced by the reaction of 1,4-dichlorobenzene and sodium sulfide may be used in coatings that come in contact with food, provided the maximum residual 1,4-dichlorobenzene levels do not exceed 0.8 ppm and other requirements are met.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 75 ppm (450 mg/m³).

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 150 ppm.

Listed as a potential occupational carcinogen.

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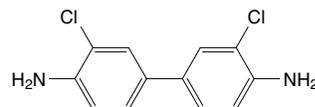
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3,3'-Dichlorobenzidine and Its Dihydrochloride**CAS Nos. 91-94-1 and 612-83-9**

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

**Carcinogenicity**

3,3'-Dichlorobenzidine and 3,3'-dichlorobenzidine dihydrochloride are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The names 3,3'-dichlorobenzidine and 3,3'-dichlorobenzidine dihydrochloride are used interchangeably in the published literature. Although only the dihydrochloride salt is believed to be available commercially, it is not always clear whether the salt or the free base was the compound studied.

Cancer Studies in Experimental Animals

3,3'-Dichlorobenzidine or its dihydrochloride caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Dietary administration of 3,3'-dichlorobenzidine caused mammary-gland cancer (adenocarcinoma) in rats of both sexes, granulocytic leukemia and Zymbal-gland cancer (carcinoma) in male rats, urinary-bladder cancer (transitional-cell or papillary transitional-cell carcinoma) in hamsters and in female dogs, and liver cancer (hepatocellular carcinoma) in female dogs (IARC 1974, Stula *et al.* 1975, 1978). Subcutaneous injection of 3,3'-dichlorobenzidine caused skin and mammary-gland tumors in rats (IARC 1974). Since 3,3'-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified. Prenatal exposure to 3,3'-dichlorobenzidine caused lymphoid leukemia (IARC 1982), and dietary exposure caused liver cancer (hepatocellular carcinoma) in males (IARC 1982, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically

to 3,3'-dichlorobenzidine or 3,3'-dichlorobenzidine dihydrochloride. In three retrospective epidemiological studies, no urinary-bladder tumors were reported in men occupationally exposed to 3,3'-dichlorobenzidine (Gerarde and Gerarde 1974, Gadian 1975, MacIntyre 1975). These studies were limited by low statistical power and short follow-up time (less than 15 years for most workers).

Since 3,3'-dichlorobenzidine was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. Three cohort studies reported an excess of bladder cancer among paperboard-printing workers (Sinks *et al.* 1992), chemical-manufacturing workers (Ouellet-Hellstrom and Rench 1996), and dye-manufacturing workers (Rosenman and Reilly 2004) who were potentially exposed to 3,3'-dichlorobenzidine; however, the workers potentially were also exposed to other substances associated with urinary-bladder cancer, such as *o*-toluidine or benzidine. One of the cohort studies (Ouellet-Hellstrom and Rench 1996) found a significant increase in the standardized incidence ratio for urinary-bladder cancer among chemical manufacturing plant workers potentially exposed to 3,3'-dichlorobenzidine who were first employed after benzidine manufacture had ended. Although pigments containing 3,3'-dichlorobenzidine were reported to have been used at the plant employing the paperboard-printing workers, exposure to 3,3'-dichlorobenzidine could not be verified by environmental measurements; this study also found an increased risk of kidney-cancer incidence and mortality (Sinks *et al.* 1992). A significant increase in cancer of the blood cells (mostly leukemia) was found among dye-manufacturing workers exposed only to 3,3'-dichlorobenzidine (Rosenman and Reilly 2004).

Properties

3,3'-Dichlorobenzidine is a chlorinated aromatic amine derived from benzidine (IARC 1974). It exists at room temperature as gray to purple needle-like crystals. It is slightly soluble in water and dilute hydrochloric acid, but readily soluble in benzene, diethyl ether, ethanol, and glacial acetic acid. Physical and chemical properties of 3,3'-dichlorobenzidine are listed in the following table.

Property	Information
Molecular weight	253.1 ^a
Melting point	132°C to 133°C ^a
Boiling point	402°C ^a
Log K_{ow}	3.51 ^a
Water solubility	0.0031 g/L at 25°C ^a
Vapor pressure	2.56×10^{-7} mm Hg at 25°C ^b
Dissociation constant (pK_a)	3.2 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

3,3'-Dichlorobenzidine is used in the United States primarily in the manufacture of pigments for printing ink, textiles, paper, paint, rubber, and plastics and as a curing agent for isocyanate-containing polymers and solid urethane plastics (IARC 1974, ATSDR 1998). As of 1983, at least seven synthetic organic pigments, toners, and lakes were produced with 3,3'-dichlorobenzidine. The yellow pigments derived from the chemical and its salts, including benzidine yellow, can be used as substitutes for the lead chromate pigments (ATSDR 1998, HSDB 2009). Use of 3,3'-dichlorobenzidine to synthesize dyes ceased in 1986 with the introduction of better dyes from other sources; however, its use in the manufacture of pigments has continued (ATSDR 1998). Both 3,3'-dichlorobenzidine and its dihydrochloride also are used in a color test for the detection of gold (IARC 1982). In addition, 3,3'-dichlorobenzidine is used in the production of tetraaminobiphenyl, which is used to produce polybenzimidazole, a thermally stable polymer used in protective clothing such as firefighters' apparel and

high-temperature gloves. 3,3'-Dichlorobenzidine has also been used as a compounding ingredient for rubber and plastics (ATSDR 1998).

Production

Commercial production of 3,3'-dichlorobenzidine in the United States began in 1938 (IARC 1974). Production volumes of 3,3'-dichlorobenzidine were considered confidential by individual companies and therefore were not available (ATSDR 1998). In 2009, 3,3'-dichlorobenzidine was produced by one manufacturer, in Europe, and the hydrochloride was produced by 10 manufacturers, including 1 each in Europe and China, 2 in East Asia, and 6 in India (SRI 2009). 3,3'-Dichlorobenzidine was available from 14 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009). The dihydrochloride is imported; imports peaked in 2000 at 8.7 million pounds, falling to 5.4 million pounds by 2008 (USITC 2009). The quantity of pigments derived from 3,3'-dichlorobenzidine totaled 129,000 lb in 1983 (ATSDR 1998). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 3,3'-dichlorobenzidine dihydrochloride totaled 1 million to 10 million pounds in 1986 and 1990 and 10 million to 50 million pounds between 1994 and 2006 (EPA 2004, 2009).

Exposure

The routes of potential human exposure to 3,3'-dichlorobenzidine are inhalation of airborne dust, ingestion of contaminated well water by those living near hazardous waste sites, and dermal contact, primarily during industrial operations. For the general population, the likelihood of exposure to 3,3'-dichlorobenzidine probably is low. Exposure via air, soil, or water is expected to be negligible, and the greatest likelihood of exposure to 3,3'-dichlorobenzidine is from improper land disposal. No current uses of 3,3'-dichlorobenzidine in commonly used consumer products were identified. In the past, exposure might have occurred during the use of pressurized spray containers of paints, lacquers, and enamels containing traces of benzidine yellow, a pigment derived from 3,3'-dichlorobenzidine (ATSDR 1998).

3,3'-Dichlorobenzidine may be released as atmospheric emissions or in wastewater during production or use as a dye intermediate. Atmospheric emissions most likely have been reduced by the adoption of closed-system operations. According to EPA's Toxics Release Inventory, environmental releases of 3,3'-dichlorobenzidine totaled 32 lb in 1999 (on-site releases), 1,000 lb in 2007, and 1,565 lb in 2008 (to off-site landfills) (TRI 2009). If released to air, 3,3'-dichlorobenzidine is expected to adsorb to particulate matter and photodegrade. If released to water, the free base will rapidly adsorb to sediment and particulate matter, where it will be bound. 3,3'-Dichlorobenzidine may undergo photolysis in water exposed to sunlight. If released to soil, it will bind to soil and possibly react with soil components. 3,3'-Dichlorobenzidine's strong tendency to partition to soils and sediments reduces the potential for human exposure (ATSDR 1998).

EPA reported in 1980 that data on the presence of 3,3'-dichlorobenzidine in the environment were limited; one survey detected 3,3'-dichlorobenzidine at concentrations of 0.13 to 3.0 mg/L at one 3,3'-dichlorobenzidine production waste-disposal site (IARC 1982). Between 1993 and 2003, 36 samples of surface water and sediment were taken from Lake Macatawa, in Holland, Michigan (Harden *et al.* 2005). Early samples contained 3,3'-dichlorobenzidine at concentrations exceeding the water-quality criteria by factors of up to 1,300; however, 3,3'-dichlorobenzidine was not detected in samples taken in 2003. Maximum concentrations of 3,3'-dichlorobenzidine in wastewater were estimated to be 10 ppb from metal finishing, 2 ppb (av-

erage = 0.3 ppb) from nonferrous metals manufacture, 10 ppb from paint and ink manufacture, and 3 ppb from coal mining (HSDB 2009).

Occupational exposure to the dihydrochloride probably continues to occur during its manufacture and conversion to derived pigments (HSDB 2009). No data were found on the number of workers potentially exposed to 3,3'-dichlorobenzidine dihydrochloride.

Regulations

Department of Transportation (DOT)

3,3'-Dichlorobenzidine is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 3,3'-Dichlorobenzidine is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: 3,3'-Dichlorobenzidine is listed as a toxic pollutant.

Water Quality Criteria: For 3,3'-dichlorobenzidine, based on fish or shellfish and water consumption = 0.021 µg/L; based on fish or shellfish consumption only = 0.028 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for 3,3'-dichlorobenzidine.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 3,3'-dichlorobenzidine = U073.

3,3'-Dichlorobenzidine is listed as a hazardous constituent of waste.

Mine Safety and Health Administration

To control airborne exposure, 3,3'-dichlorobenzidine shall not be used or stored except by competent persons under laboratory conditions approved by a nationally recognized agency acceptable to the Secretary.

Occupational Safety and Health Administration (OSHA)

3,3'-Dichlorobenzidine is listed as a potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure to 3,3'-dichlorobenzidine by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

3,3'-Dichlorobenzidine and its salts are listed as potential occupational carcinogens.

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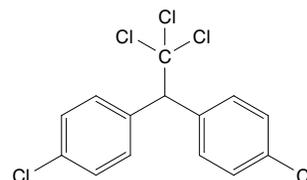
Dichlorodiphenyltrichloroethane

CAS No. 50-29-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as DDT or 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane



Carcinogenicity

Dichlorodiphenyltrichloroethane (DDT) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

DDT caused liver tumors in two rodent species and by two different routes of exposure. It caused primarily malignant primary liver-cell tumors (hepatocellular carcinoma) in mice of both sexes and in rats (of unspecified sex) following dietary exposure; in mice of both sexes following administration by stomach tube; and in female mice following subcutaneous injection (reviewed by IARC 1991). Increased incidences of lung tumors and malignant lymphoma following oral exposure to DDT were observed in some, but not all, of the studies in mice.

Cancer Studies in Humans

No epidemiological studies of the carcinogenicity of DDT in humans were identified at the time DDT was listed in the *Fourth Annual Report on Carcinogens*. Since then, a number of epidemiological studies of human cancer and DDT exposure have been identified. Studies

reviewed in 1991 by the International Agency for Research on Cancer were inconclusive because of coexposure to numerous pesticides and the small sizes of the study groups (IARC 1991).

Epidemiological studies conducted since 1991 have mainly been case-control or nested case-control studies, plus a few prospective or occupational cohort studies, and include over 20 studies of breast cancer. Comparison of the results of breast-cancer studies has been complicated by differences in exposure assessment, dietary factors, breast-tumor type and estrogen-receptor status, age, menopausal status, lactation history, body mass status, race or ethnicity, or exposure to other potential carcinogens (Snedeker 2001, Calle *et al.* 2002, Clapp *et al.* 2008, Eskenazi *et al.* 2009). The majority of breast-cancer studies (mostly of older women in the United States) did not find statistically significant associations with estimated exposure or with serum or adipose-tissue levels of DDT or 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (DDE, a metabolite of DDT) (see reviews above and ATSDR 2002, 2008, Lopez-Cervantes *et al.* 2004). However, positive associations between DDT exposure and breast cancer were reported in a few studies among women with higher levels of exposure and among certain subgroups of women (Wolff *et al.* 1993, Hoyer *et al.* 2000, Romieu *et al.* 2000, Rubin *et al.* 2006, Cohn *et al.* 2007).

Several studies have investigated the association between DDT or DDE exposure and cancer at other tissue sites. One study reported an association between DDT exposure and leukemia among agricultural workers (Morris-Brown *et al.* 1990). Increased risk or incidence of multiple myeloma with DDT exposure was found in a case-control study of farmers (Eriksson and Karlsson 1992) and a cohort proportionate-mortality study of pesticide applicators who had used 94% DDT (Cocco *et al.* 1997). Increased risk of liver cancer also has been associated with serum DDT level (McGlynn *et al.* 2006), DDT pesticide application (Cocco *et al.* 1997), and levels of DDE in adipose tissue (Cocco *et al.* 2000). Increased risks of cancer at other tissue sites, such as the gallbladder (Shukla *et al.* 2001), prostate (Settimi *et al.* 2003), and testes (McGlynn *et al.* 2008), have been reported in one study for each site.

Properties

DDT is a chlorinated aromatic hydrocarbon insecticide (NCI 1978) that in its pure form exists at room temperature as colorless to off-white needles or powder with a slight aromatic odor (Akron 2009, HSDB 2009). It is practically insoluble in water, but it is soluble in many organic solvents, including acetone, benzene, benzyl benzoate, carbon tetrachloride, chlorobenzene, cyclohexanone, ethanol, ethyl ether, gasoline, isopropanol, kerosene, morpholine, peanut oil, pine oil, tetralin, and tributyl phosphate (IARC 1974, HSDB 2009). DDT is highly soluble in lipids (HSDB 2009). It is very stable and exceptionally persistent in the environment (IPCS 1989). Technical-grade DDT is a mixture of three forms, *p,p'*-DDT (85%), *o,p'*-DDT (15%), and *o,o'*-DDT (trace amounts) (ATSDR 2002). Technical-grade DDT may also contain DDE and 1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethane (DDD) as contaminants; both are breakdown products of DDT. Physical and chemical properties of DDT are listed in the following table.

Property	Information
Molecular weight	354.5
Specific gravity	0.98 to 0.99
Melting point	108.5°C
Boiling point	260°C
Log K_{ow}	6.91
Water solubility	5.50×10^{-6} g/L at 25°C
Vapor pressure	1.6×10^{-7} mm Hg at 20°C

Source: HSDB 2009.

Use

DDT was first used in the United States as an insecticide in 1939 (ATSDR 2002). From 1946 to 1972, DDT was one of the most widely used insecticides in the world (HSDB 2009). It was used for the control of insect pests such as the pink bollworm on cotton, codling moth on deciduous fruits, Colorado potato beetle, and European corn borer (ATSDR 2002). In the public health field, DDT was used to control malaria, typhus, and other insect-transmitted diseases and to treat body lice (HSDB 2009). It was also used for mothproofing clothing (ATSDR 2002). Its usage peaked in the 1960s, but in 1972, it was banned for the vast majority of uses in the United States (ATSDR 2002, HSDB 2009). DDT is currently used in the United States only under Public Health Service supervision for public health emergencies and by the U.S. Department of Agriculture or U.S. military for health quarantine. It is also still used in many countries where malaria is endemic, as an insecticide to control mosquitoes (HSDB 2009).

Production

Technical DDT was first synthesized in 1874, and commercial production in the United States had begun by 1945 (ATSDR 2002, HSDB 2009). In 1962, 82 million kilograms (180.4 million pounds) of DDT was produced in the United States for use on 334 agricultural commodities. In 1971, production in the United States was estimated at 2 million kilograms (4.4 million pounds) (ATSDR 2002). In 2009, no U.S. companies manufactured DDT, but it was produced by six companies worldwide, including one in Europe, two in China, one in East Asia, and two in India (SRI 2009), and was available from 21 suppliers, including 9 U.S. suppliers (Chem Sources 2009). DDT is no longer imported into the United States (ATSDR 2002); it was last imported in 1972, in the amount of about 200 metric tons (441,000 lb) (HSDB 2009). In 1978 (the last year for which export data specific to DDT were available), U.S. exports of DDT were 13.7 million kilograms (30.2 million pounds).

Exposure

Despite the 1972 U.S. ban of DDT, human exposure continues because of its extensive former use, its current use in some areas of the world, and the persistence of DDT and its breakdown products in the environment (ATSDR 2002). DDT is still released into the atmosphere through spraying in some areas of the world. In addition, it volatilizes from soil in areas where it was formerly used. The volatilization and deposition cycle may be repeated many times, resulting in widespread distribution of DDT worldwide. In addition, DDT readily accumulates in animal fat and thus bioaccumulates through the food chain. DDT and its breakdown products have been found throughout the world, from the Arctic to the Antarctic, having been detected in ambient and indoor air, precipitation (rain and snow), water, soil, and animal and plant tissues. The residual levels of DDT in the environment have declined and continue to decline, but because of DDT's high persistence, it will be present at low levels for decades. In a study of long-term dietary intake of DDT and all of its metabolites, daily intake for a 70-kg 16-year-old U.S. male was estimated at 6.5 µg for 1978–79, 2.4 µg for 1979–80, 1.5 µg for 1984–86, and 0.97 µg for 1986–91. Currently, human exposure to DDT and its breakdown products is primarily through dietary ingestion, particularly of meat, fish, poultry, and root and leafy vegetables. The highest dietary exposure occurs among indigenous Arctic populations that eat traditional foods such as seal, whale, or caribou. The highest average daily intake was observed in the eastern Arctic, where total daily intake of DDT and all of its metabolites was 24.2 to 27.8 µg/day. The foods contributing the most were beluga whale blubber (316 µg/g of wet weight) and narwhal whale blubber (273 µg/g) (ATSDR 2002).

DDT has been measured in numerous human tissues in the U.S. population and in other populations around the world, including indigenous Arctic peoples. DDT accumulates in fatty tissues and is usually found in higher concentrations in human milk than in cow's milk or other infant foods. In the United States, mean concentrations of DDT were 0.99 mg/kg (990 ng/g) in milk fat from Arkansas women in 1986, 28.8 ppb (ng/g) in serum from consumers of Great Lakes fish in 1982, and 252 ng/g in adipose tissue from a national sample of individuals age 45 years or older in 1986 (ATSDR 2002). The median concentration of DDT in plasma samples from 407 highly exposed Inuit individuals living in Greenland was 35 µg/kg of lipid (35 ng/g) (Bjerregaard *et al.* 2001). DDT was detected in 95% of the samples from this population. For the population measured in the United States National Health and Nutrition Examination Survey (NHANES), the geometric mean concentration of DDE in serum was 260 ng/g of lipid in 1999–2000, 285 ng/g in 2001–02, and 238 ng/g in 2003–04 (ATSDR 2008). The Mexican-American population sampled in NHANES had mean DDE concentrations about twice those for the total population: 674 ng/g in 1999–2000, 652 ng/g in 2001–02, and 444 ng/g in 2003–04.

Regulations

Department of Transportation (DOT)

DDT is considered a hazardous substance and a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material, including transporting it in tank cars.

Environmental Protection Agency (EPA)

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00022 µg/L; based on fish or shellfish consumption only = 0.00022 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Federal Insecticide, Fungicide, and Rodenticide Act

Registrations for nearly all uses of DDT have been cancelled.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of DDT = U061.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Action levels for DDT in various food items and in processed animal feed range from 0.05 to 5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 mg/m³.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 500 mg/m³.

Recommended exposure limit (time-weighted-average workday) = 0.5 mg/m³.

Listed as a potential occupational carcinogen.

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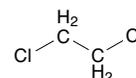
1,2-Dichloroethane

CAS No. 107-06-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as ethylene dichloride



Carcinogenicity

1,2-Dichloroethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,2-dichloroethane caused tumors in mice and rats at several different tissue sites. Administration of 1,2-dichloroethane by stomach tube caused malignant lymphoma and benign lung tumors (alveolar/bronchiolar adenoma) in mice of both sexes, blood-vessel cancer (hemangiosarcoma) in rats of both sexes, mammary-gland cancer (adenocarcinoma) in female mice and rats, uterine cancer (endometrial stromal tumors) in female mice, forestomach cancer (squamous-cell carcinoma) in male rats, and liver cancer (hepatocellular carcinoma) in male mice (NCI 1978).

Since 1,2-dichloroethane was listed in the *Second Annual Report on Carcinogens*, an additional study in rodents has been identified. In mice and rats, inhalation exposure to 1,2-dichloroethane caused mammary-gland tumors in both species and liver and lung tumors in mice (IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,2-dichloroethane. Since 1,2-dichloroethane was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer reviewed five cohort mortality studies and one nested case-control study of chemical workers with exposure to 1,2-dichloroethane and other chemicals (such as ethylene oxide or chlorohydrin) (IARC 1999). Excesses of lymphatic and hematopoietic cancer were observed in three cohort studies (Hogstedt *et al.* 1979, Benson and Teta 1993, Olsen *et al.* 1997), pancreatic cancer in one study (Benson and Teta 1993), and stomach cancer in one study (Hogstedt *et al.* 1979). No excesses of cancer were found in a fourth cohort study (Sweeney *et al.* 1986) or in a cohort study of brain cancer with a nested case-control study (Austin and Schnatter 1983a,b). Because all of the workers in these studies potentially were coexposed to numerous agents, it is not possible to evaluate excess risks associated specifically with exposure to 1,2-dichloroethane.

Properties

1,2-Dichloroethane is a chlorinated aliphatic hydrocarbon that exists at room temperature as a colorless oily liquid with a sweet, pleasant odor similar to that of chloroform (HSDB 2009). It is slightly soluble in water, soluble in acetone, benzene, and carbon tetrachloride, and miscible with alcohol, chloroform, and ether. 1,2-Dichloroethane is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 1,2-dichloroethane are listed in the following table.

Property	Information
Molecular weight	99.0 ^a
Specific gravity	1.2351 at 20°C ^a
Melting point	-35.3°C ^a
Boiling point	83.5°C ^a
Log <i>K</i> _{ow}	1.48 ^a
Water solubility	8.6 g/L at 25°C ^a
Vapor pressure	78.9 mm Hg at 25°C ^a
Vapor density relative to air	3.42 ^b

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

1,2-Dichloroethane is currently used primarily to produce vinyl chloride (IPCS 1995, IARC 1999). It was formerly used as a solvent for processing pharmaceutical products; as a solvent for fats, oils, waxes, gums, resins, and particularly for rubber; and in paint, varnish, and finish removers (HSDB 2009). It was also used as an insect fumigant for stored grains and in mushroom houses, a soil fumigant in peach and apple orchards, a cleaner for upholstery and carpets, a solvent in textile cleaning and metal degreasing, a lead scavenger in antiknock gasoline, a starting material for chlorinated solvents such as vinylidene chloride, a dispersant for plastics and elastomers such as synthetic rubber, an ore flotation compound, and an extractant in certain food processes (NIOSH 1978, IARC 1979, HSDB 2009). It has been replaced as a solvent and degreaser by less toxic compounds and is no longer registered for use as an insect fumigant in the United States (IARC 1999). Therapeutically, 1,2-dichloroethane formerly was used as a general anesthetic instead of chloroform, especially in ophthalmic surgery (HSDB 2009).

Production

U.S. commercial production of 1,2-dichloroethane was first reported in 1922 (IARC 1979). 1,2-Dichloroethane is a major industrial chemical and ranks among the highest-volume chemicals produced in the United States (EPA 2009a). In 2003, total U.S. annual production capacity for 1,2-dichloroethane was over 35 billion pounds (CMR 2003). In 2009, 1,2-dichloroethane was produced by 95 manufacturers worldwide, including 15 in the United States (SRI 2009), and was available from 67 suppliers, including 35 U.S. suppliers (Chem Sources 2009). U.S. imports of 1,2-dichloroethane peaked at 155 million kilograms (341 million pounds) in 1999, declining to 498,000 kg (1 million pounds) in 2007 and rebounding to 44 million kilograms (96 million pounds) in 2008 (USITC 2009). U.S. exports of 1,2-dichloroethane also peaked in 1999, at 1.2 billion kilograms (2.6 billion pounds), falling to a low of 398 million kilograms (875 million pounds) in 2006. Reports filed every four years under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,2-dichloroethane totaled over a billion pounds from 1986 to 2006 (EPA 2004, 2009b).

Exposure

The routes of potential human exposure to 1,2-dichloroethane are inhalation, ingestion, and dermal contact (IARC 1979). For the general population, the greatest source of exposure is inhalation of contaminated ambient or indoor air, with a minor contribution from ingestion of contaminated drinking water. Releases to the environment may result from the manufacture, use, storage, distribution, and disposal of 1,2-dichloroethane (ATSDR 2001). 1,2-Dichloroethane is also an anaerobic biodegradation product of tetrachloroethane. According to EPA's Toxics Release Inventory, environmental releases of 1,2-dichloroethane peaked in 1990, at 6,525,967 lb, over 5.6 million pounds (85%) of which was released to air. In 2007, 56 facilities released a total of 450,400 lb of 1,2-dichloroethane, of which 334,000 lb (74%) was released to air, 96,568 lb (21%) to land, 17,000 lb (4%) to on-site and off-site underground injection wells, and 2,310 lb (0.5%) to water (TRI 2009). 1,2-Dichloroethane was identified in at least 570 of the 1,585 hazardous-waste sites proposed for inclusion on EPA's National Priorities List; however, the number of sites evaluated for 1,2-dichloroethane was not reported (ATSDR 2001).

1,2-Dichloroethane has been detected in ambient air (urban and rural) and indoor air of residences near hazardous-waste disposal sites and in surface water, groundwater, and drinking water (ATSDR 2001). In the 1980s, mean concentrations of 1,2-dichloroethane in U.S. am-

bient air ranged from 0.33 to 6.05 $\mu\text{g}/\text{m}^3$ (IPCS 1998). EPA reported that 1,2-dichloroethane was present in 53 of 204 surface-water samples taken near heavily industrialized areas across the United States (IARC 1979). Drinking-water samples from a number of urban and rural locations in the United States have been reported to be contaminated with 1,2-dichloroethane. Concentrations in sources of drinking-water supplies were reported to range from trace amounts to 4.8 $\mu\text{g}/\text{L}$ in surface water and from trace amounts to 400 $\mu\text{g}/\text{L}$ in groundwater. Ingestion of 1,2-dichloroethane in contaminated drinking water is expected to be an important source of exposure for 4% to 5% of the U.S. population. 1,2-Dichloroethane has also been detected in food items and in human breath, urine, and milk (ATSDR 2001).

Occupational exposure to 1,2-dichloroethane now occurs chiefly among workers involved in the production of vinyl chloride (IPCS 1998). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 83,246 workers in 1,526 plants, including 33,361 women, potentially were exposed to 1,2-dichloroethane (NIOSH 1990). The largest numbers of exposed workers were employed in the Chemical and Allied Products, Apparel and Other Textile Products, Business Services, and Petroleum and Coal Products industries as machine operators, assemblers, production inspectors, checkers, and examiners (ATSDR 2001).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,2-dichloroethane on ships and barges.

Department of Transportation (DOT)

1,2-Dichloroethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 1,2-dichloroethane is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Designated a hazardous substance.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.38 $\mu\text{g}/\text{L}$; based on fish or shellfish consumption only = 37 $\mu\text{g}/\text{L}$.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxic characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,2-dichloroethane = U077, F024, F025, K018, K019, K020, K029, K030, K096.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 ppm.

Ethylene dichloride in spice oleoresins when present as a residue from the extraction of spice is allowed in concentrations not to exceed 30 ppm.

Ethylene dichloride residues shall not exceed 150 ppm when used in the production of modified hop extract used in beer.

Ethylene dichloride residues shall not exceed 250 ppm when used as a solvent in the production of the food additive whole fish protein concentrate.

Polyethylenimine polymer may be used as a fixing material in the immobilization of glucoamylase enzyme for use in the manufacture of beer, with residual 1,2-dichloroethane levels not to exceed 1 ppm.

The maximum quantity of ethylene dichloride permitted to remain in or on the extracted by-products in the manufacture of animal feeds is 300 parts per million.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Acceptable peak exposure = 200 ppm (maximum duration = 5 min in any 3 h).

Ceiling concentration = 100 ppm.

Permissible exposure limit (PEL) = 50 ppm.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm.

Recommended exposure limit (time-weighted-average workday) = 1 ppm (4 mg/m³).

Short-term exposure limit (STEL) = 2 ppm (8 mg/m³).

Listed as a potential occupational carcinogen.

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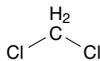
Dichloromethane

CAS No. 75-09-2

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as methylene chloride



Carcinogenicity

Dichloromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to dichloromethane by inhalation caused tumors in two rodent species and at several different tissue sites. In mice of both sexes, it caused tumors of the lung (alveolar/bronchiolar tumors) and liver (hepatocellular tumors), and in rats of both sexes, it caused benign mammary-gland tumors (fibroadenoma) (NTP 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dichloromethane (IARC 1982). In 1999, the International Agency for Research on Cancer reviewed additional epidemiological studies published after dichloromethane had been listed in the *Fifth Annual Report on Carcinogens*, including seven cohort studies (six of which were small) and three case-control studies (of brain cancer, breast cancer, and rectal plus lung cancer). Although cancer risk was increased for some tissue sites, including the pancreas in two cohort studies, the breast in one case-control and one cohort study, and the liver, prostate, rectum, and brain in one study each, IARC concluded that the evidence for carcinogenicity was too inconsistent to support a causal interpretation (IARC 1987, 1999). Studies published since the IARC review include updates of previous studies (Hearne and Pifer 1999, Dumas *et al.* 2000, Radican *et al.* 2008) and new case-control studies of brain cancer (Cocco *et al.* 1999), lymphoma (Seidler *et al.* 2007), and renal-cell cancer (Dosemeci *et al.* 1999). As was found in the 1999 IARC review, excesses of cancer at specific tissue sites, including the pancreas, lymphohematopoietic system, brain and central nervous system, and breast, were reported in some but not all studies.

Properties

Dichloromethane is a chlorinated hydrocarbon that exists at room temperature as a colorless liquid with a sweet, pleasant odor similar to that of chloroform (NTP 1986). It is miscible with alcohol, ether, dimethyl formamide, and carbon tetrachloride. Dichloromethane is stable at normal temperatures and pressures, but it may form explosive compounds when in a high-oxygen environment (Akron 2009). Physical and chemical properties of dichloromethane are listed in the following table.

Property	Information
Molecular weight	84.9
Specific gravity	1.3255 20°C/4°C
Melting point	-95°C
Boiling point	39.75°C at 760 mm Hg
Log K_{ow}	1.25
Water solubility	13.0 g/L at 25°C
Vapor pressure	435 mm Hg at 25°C
Vapor density relative to air	2.93

Source: HSDB 2009.

Use

Dichloromethane is used as a solvent in paint strippers and removers (30%), in adhesives (20%), as a propellant in aerosols (10%), as a solvent in the manufacture of pharmaceuticals and drugs (10%), in chemical processing (10%), as a metal cleaning and finishing solvent (10%), and in urethane foam blowing (5%) (Holbrook 2003). Other uses make up the remaining 5%. Dichloromethane has also been used as a solvent in the production of triacetate fibers, in film processing, and as an extraction solvent for spice oleoresins, hops, and caffeine in coffee (NTP 1986). However, due to health concerns, dichloromethane's use as an extraction solvent in food products and coffee has declined greatly over the years (ATSDR 2000). It is also used as a low-pressure refrigerant, for air-conditioning installations, and as a low-temperature heat-transfer medium (Holbrook 2003). Current household products that may contain dichloromethane include lubricants, valve cleaners, and degreasers for automobiles, adhesive and varnish removers, paint strippers, and one household herbicide (HPD 2009). Dichloromethane is present in these products at percentages ranging from 1% to 90%. Dichloromethane was once registered for use in the United States as an insecticide for commodity fumigation of strawberries, citrus fruits, and a variety of grains (ATSDR 2000). It is no longer an active ingredient in any registered pesticide product in the United States (HSDB 2009).

Production

In 2009, dichloromethane was produced by 26 manufacturers worldwide, including 4 in the United States (SRI 2009), and was available from 133 suppliers, including 58 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of dichloromethane totaled 500 million to 1 billion pounds in 1986 and 1990 and 100 million to 500 million pounds between 1996 and 2006 (EPA 2004, 2009). From 1989 to 2008, U.S. exports of dichloromethane exceeded imports; in 2008, imports were over 19.8 million pounds, and exports were 136.9 million pounds (USITC 2009).

Exposure

The routes of potential human exposure to dichloromethane are inhalation, ingestion, and dermal contact (NTP 1986). However, absorption is slower after dermal contact than after ingestion or inhalation. The general population is exposed mainly through inhalation of ambient air. Inhalation exposure might also occur through the use of consumer products containing dichloromethane, such as paint removers, which results in relatively high concentrations in indoor air (IPCS 1996, ATSDR 2000). Dichloromethane was found in 43.7% of 1,159 consumer household products tested and in 74.3% of paint-related products, at an average concentration of 33.5% (Sack *et al.* 1992). According to EPA's Toxics Release Inventory, environmental releases of dichloromethane totaled nearly 139 million pounds in 1988. In 2007, over 5.9 million pounds was released by 297 facilities, including over 5 million pounds to air, for a decrease of over 95% since 1988 (TRI

2009). In rural and remote areas, dichloromethane was measured in ambient air at concentrations of 0.07 to 0.29 $\mu\text{g}/\text{m}^3$; in suburban areas, the average concentration was less than 2 $\mu\text{g}/\text{m}^3$, while in urban areas it was no more than 15 $\mu\text{g}/\text{m}^3$. Near hazardous-waste sites, concentrations of up to 43 $\mu\text{g}/\text{m}^3$ were recorded (IPCS 1996).

Dichloromethane occurs in groundwater, finished drinking water, commercially bottled artesian-well water, and surface water in heavily industrialized river basins. Higher levels of dichloromethane typically are found in groundwater than surface water. Dichloromethane was the sixth most frequently detected organic contaminant in groundwater from hazardous-waste sites in 1987, occurring at 19% of the sites (ATSDR 2000). In a study published in 2007, dichloromethane was detected in 3% of over 5,000 groundwater samples taken in the United States between 1985 and 2002. The concentrations ranged from 0.02 to 100 $\mu\text{g}/\text{L}$, with a median well below the Safe Drinking Water Act maximum contaminant level of 5 $\mu\text{g}/\text{L}$ (Moran *et al.* 2007).

Occupational exposure to dichloromethane occurs during its production and shipping, primarily during filling and packaging. Because of its use in paint strippers, exposure also occurs during formulation of paint removers, original equipment manufacture, and commercial furniture refinishing (IPCS 1996). In the 1980s, dichloromethane was found in the air at an Israeli workplace at a concentration of 5.22 ppm and in urine samples from seven workers at a maximum concentration of 0.06 mg/L (Hoffer *et al.* 2005). In the 1990s, health-hazard investigations by the National Institute for Occupational Safety and Health found workplace air concentrations of 0.17 ppm to 525 ppm, with a median of 5 ppm (Armstrong and Green 2004). In field monitoring of workers in a waste-repackaging facility, dichloromethane was detected in 7 of 16 samples of exhaled breath at concentrations of up to 573 ppm (Thrall *et al.* 2001). In 2003, the American Conference of Governmental Industrial Hygienists recommended that a urinary concentration of 200 $\mu\text{g}/\text{L}$ at the end of a shift be used to monitor the threshold limit value of 50 ppm in workplace air (Imbriani and Ghittori 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,438,196 workers, including 352,536 women, potentially were exposed to dichloromethane (NIOSH 1990). No more recent large occupational exposure surveys were identified.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of dichloromethane on ships and barges.

Consumer Product Safety Commission (CPSC)

Products containing dichloromethane must be labeled to indicate that inhalation of vapor has produced cancer in laboratory animals and must also specify precautions.

Department of Transportation (DOT)

Dichloromethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 4.6 $\mu\text{g}/\text{L}$; based on fish or shellfish consumption only = 590 $\mu\text{g}/\text{L}$.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of dichloromethane = U080, F001, F002, F024, F025, K009, K010, K156, K157, K158.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.

Dichloromethane may be used as an extraction solvent to prepare modified hop extract, spice oleoresins, and coffee, with limitations prescribed in 21 CFR 172 and 173.

Dichloromethane is banned from use in cosmetic products.

Polycarbonate resins may be safely used in articles intended for use in producing, packaging, or holding foods with residual methylene chloride levels not to exceed 5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 25 ppm.

Short-term exposure limit (STEL) = 125 ppm.

Comprehensive standards for occupational exposure to this substance have been developed.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 50 ppm.

Consumer Products Safety Commission (CPSC)

Requests that manufacturers eliminate the use of hazardous chemicals, including dichloromethane, in children's products.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 2,300 ppm.

Listed as a potential occupational carcinogen.

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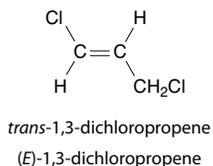
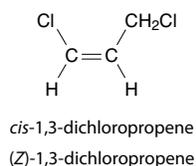
1,3-Dichloropropene (Technical Grade)

CAS No. 542-75-6

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as Telone II soil fumigant, a registered trademark of Dow Agrosciences



Carcinogenicity

Technical-grade 1,3-dichloropropene (containing 1.0% epichlorohydrin as a stabilizer) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. The technical-grade 1,3-dichloropropene used in the cancer studies in experimental animals was a mixture of *cis*- and *trans*-isomers and varied in purity and the stabilizer used (see Properties).

Cancer Studies in Experimental Animals

Oral exposure to technical-grade 1,3-dichloropropene (Telone II, approximately 89% pure, containing 1.0% epichlorohydrin as a stabilizer) caused tumors at several different tissue sites in rats and mice. Administered by stomach tube, technical-grade 1,3-dichloropropene caused benign and/or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma) in rats of both sexes and in female mice. It also caused urinary-bladder cancer (transitional-cell carcinoma) and benign lung tumors (alveolar/bronchiolar adenoma) in female mice and benign liver tumors (adenoma) in male

mice. The same types of tumors observed in female mice (forestomach, urinary-bladder, and lung tumors) also were observed in male mice; however, the evidence for carcinogenicity in males was considered to be inadequate because of low survival in the vehicle-control group (NTP 1985). *cis*-1,3-Dichloropropene administered by subcutaneous injection caused tumors at the injection-site (fibrosarcoma) in female mice (Van Duuren *et al.* 1979).

Since technical-grade 1,3-dichloropropene was listed in the *Fifth Annual Report on Carcinogens*, studies in rodents have been identified that evaluated the carcinogenicity of technical-grade 1,3-dichloropropene without the stabilizer epichlorohydrin. Inhalation exposure to technical-grade 1,3-dichloropropene (92.1% pure, stabilized with 2% epoxidized soybean oil) caused benign lung tumors (alveolar/bronchiolar adenoma) in male mice (Lomax *et al.* 1989, IARC 1999). Dietary exposure to 1,3-dichloropropene (Telone II, 96% pure, stabilized with 2% epoxidized soybean oil) microencapsulated in a starch-sucrose matrix caused benign liver tumors (hepatocellular adenoma) in rats of both sexes (Stebbins *et al.* 2000).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,3-dichloropropene. Two cases of malignant histiocytic lymphoma were reported among nine firemen accidentally exposed to 1,3-dichloropropene six years before diagnosis, and one case of leukemia was reported in a farmer exposed to 1,3-dichloropropene (IARC 1986, 1987). Since technical grade 1,3-dichloropropene was listed in the *Fifth Annual Report on Carcinogens*, an ecological case-control study of pancreatic cancer mortality (from 1989 to 1996) and exposure to organochlorine pesticides was reported. The authors reported an increase in pancreatic cancer mortality among long-term residents in areas with high application rates of 1,3-dichloropropene after adjustment for the use of other pesticides (Clary and Ritz 2003).

Properties

1,3-Dichloropropene, a chlorinated alkene, exists at room temperature as a clear colorless to straw-colored liquid with a chloroform-like odor (NTP 1985, IARC 1986). It is slightly soluble in water and soluble in methanol, chloroform, acetone, diethyl ether, toluene, benzene, *n*-heptane, and octane. It is stable at normal temperatures in closed containers, but is considered highly flammable (Akron 2009). Technical-grade formulations of 1,3-dichloropropene contain mixtures of *cis* (Z) and *trans* (E) isomers (EPA 2000). Physical and chemical properties of 1,3-dichloropropene are listed in the following table.

Property	Technical	Cis	Trans
Molecular weight	111.0	111.0	111.0
Specific gravity	1.220 at 25°C	1.224 at 20°C	1.224 at 20°C
Melting point	< -50°C	NR	NR
Boiling point	108°C	104°C	112°C
Log <i>K</i> _{ow}	1.82	2.06	2.03
Water solubility	2.8 g/L at 20°C	2.7 g/L at 25°C	2.8 g/L at 25°C
Vapor pressure	34 mmHg at 25°C	26 mmHg at 20°C	34 mmHg at 25°C
Vapor density relative to air	3.8	1.4	1.4

Source: HSDB 2009. NR = not reported.

The technical-grade formulation of 1,3-dichloropropene (Telone II) used in the National Toxicology Program cancer studies in rodents contained 88% to 90% 1,3-dichloropropene (41.6% *cis*, 45.9% *trans*), 2.5% 1,2-dichloropropene, 1.5% of a trichloropropene isomer, other impurities, and 1% epichlorohydrin as stabilizer (NTP 1985). The inhalation-exposure study (Lomax *et al.* 1989) used a formulation

containing 92.1% 1,3-dichloropropene (49.5% *cis*, 42.6% *trans*), 0.7% 1,2-dichloropropane, and mixtures of hexanes and hexadienes, stabilized with 2% epoxidized soybean oil. The formulation used in the dietary-exposure study (Stebbins *et al.* 2000) contained 96% 1,3-dichloropropene (50.7% *cis*, 45.1% *trans*), stabilized with 2% epoxidized soybean oil; no information on impurities was reported. Other formulations of pesticides based on 1,3-dichloropropene may also contain 1,2-dichloropropane, trichloronitromethane, 1,2-dibromoethane, or methyl isothiocyanate (IARC 1986, HSDB 2009).

Use

1,3-Dichloropropene (a technical-grade mixture of the *cis*- and *trans*-isomers) is used as a preplanting fumigant, mainly for the control of nematodes affecting the roots of plants, selected plant diseases, garden centipedes, wireworms, and weeds; as a solvent; and as an intermediate in the manufacture of 3,3-dichloro-1-propene and other pesticides. It is registered for use on all vegetable, fruit, and nut crops, all forage crops, tobacco, all fiber crops, and all nursery crops (EPA 1998). In Hawaii, 1,3-dichloropropene is used to control nematodes on pineapples at planting (Albrecht 1987). In 2009, three products containing 1,3-dichloropropene as an active ingredient were registered for restricted, non-residential use in the United States (EPA 2009). No products containing 1,3-dichloropropene are registered for use by homeowners (EPA 1998).

Production

1,3-Dichloropropene was first synthesized in 1872, and commercial production in the United States started in 1955 (NTP 1985, IARC 1986). Before 1978, annual U.S. production was 25 million kilograms (55 million pounds) (NTP 1985). In 2009, 1,3-dichloropropene was produced by one manufacturer each in the United States and East Asia and two manufacturers in Europe (SRI 2009) and was available from 21 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,3-dichloropropene or Telone II were found. Reports filed from 1986 to 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,3-dichloropropene totaled 1 million to 10 million pounds (EPA 2004).

Exposure

The primary routes of potential human exposure to 1,3-dichloropropene are inhalation, dermal contact, and ingestion (NTP 1985, ATSDR 1992, EPA 1998). In 1978, 1 million kilograms (2.2 million pounds) of pesticide containing 1,3-dichloropropene was reportedly used in California (ATSDR 1992). In Hawaii, estimated usage on pineapple fields based on the usual application rate for Telone II was nearly 0.9 million kilograms (2 million pounds) in 1985 (Albrecht 1987). Although the data are incomplete, it has been estimated that from 1987 to 1995, over 23 million pounds of 1,3-dichloropropene was applied as a soil fumigant nationwide (EPA 1998). 1,3-Dichloropropene has not been detected in food crops grown in treated soils.

EPA's Toxics Release Inventory reported environmental releases of almost 55,000 lb of 1,3-dichloropropene in 1988. Releases have steadily declined since then; in 2009, 16 industrial facilities released 5,695 lb. Most releases have been to air (TRI 2009). 1,3-Dichloropropene can also be formed from chlorination of organic material during water treatment. In air, 1,3-dichloropropene is degraded by photochemically produced hydroxyl radicals, with a half-life of 7 hours for the *trans*-isomer and 12 hours for the *cis*-isomer. It is also degraded by reaction with ozone, with a half-life of 12 to 52 days. Volatilization of 1,3-dichloropropene from a model river was estimated to occur with a half-life of 4 hours (HSDB 2009). In field studies, 25% of

1,3-dichloropropene volatilized within two weeks after soil injection (EPA 1998). The 1,3-dichloropropene remaining in moist soils may hydrolyze at rates depending on temperature; the reported half-life was 13.5 days at 20°C, 2 days at 29°C, and 100 days at 2°C. Absorption by soil and sediment is expected to be low, based on physical and chemical properties and laboratory data. Monitoring data show that 1,3-dichloropropene is highly mobile in soils (ATSDR 1992, EPA 1998, HSDB 2009). Biodegradation by *Pseudomonas* spp. is expected to occur in soil, with a half-life of 1 to 3 days (NTP 1985). Hydrolysis and biodegradation products are mostly 3-chloroallyl alcohol and, to a lesser extent, 3-chloroacrylic acid (NTP 1985, ATSDR 1992, EPA 1998). The potential for 1,3-dichloropropene or its degradation products to bioaccumulate in terrestrial or aquatic organisms is low, based on physical and chemical properties. This is consistent with the finding that only 1% of radiolabeled 1,3-dichloropropene administered orally remained in rats after 4 days (NTP 1985, HSDB 2009).

1,3-Dichloropropene was measured in ambient air at distances of 0 to 800 m from treated fields at mean seven-day air concentrations ranging from 11 to 181 µg/m³ (EPA 1998). In another study, the median air concentration of *cis*-1,3-dichloropropene was 23.9 ppb by volume in 148 urban air samples collected from representative locations (ATSDR 1992). During field application of the nematocide in the Netherlands, 8-hour time-weighted-average concentrations were up to 1,120 µg/m³ for the *cis*-isomer and 910 µg/m³ for the *trans*-isomer (van Welie *et al.* 1991). 1,3-Dichloropropene was measured in a drinking-water aquifer at average concentrations of up to 357 ppb (micrograms per liter) and in surface water at up to 1.8 ppb (EPA 1998). It was detected at very low levels (up to 18 µg/L) in groundwater contaminated by leachates from municipal landfills and was identified at 107 hazardous-waste sites on EPA's National Priorities List (ATSDR 1992). Samples of rainwater were reported to contain up to 12 ng/L of 1,3-dichloropropene (10 ng/L of the *cis*-isomer and 2 ng/L of the *trans*-isomer). In one study, water entering a treatment facility did not contain detectable levels of 1,3-dichloropropene, but after chlorination, 1,3-dichloropropene was found in the resulting liquid sludge at a concentration of 10 ppb (HSDB 2009).

Workers may be exposed to 1,3-dichloropropene during its manufacture or during formulation or application of the pesticide products. Measured exposure of agricultural workers was highest during loading (mean concentration = 10,833 µg/m³) and lower during application (mean concentration = 1,359 µg/m³) (EPA 1998). Dermal exposure has been shown to occur even with the use of most types of protective gloves (Zainal and Que Hee 2005). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,162 workers, including 33 women, potentially were exposed to 1,3-dichloropropene in the Chemical, Petroleum, and Coal Products industries (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for the safe transport of 1,3-dichloropropene on ships and barges.

Department of Transportation (DOT)

Dichloropropenes are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.34 µg/L; based on fish or shellfish consumption only = 21 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerance for the combined residues of the fungicide *cis*- and *trans*-1,3-dichloropropene on grapes = 0.018 ppm.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,3-dichloropropene = U084.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = 1 ppm (5 mg/m³).

Listed as a potential occupational carcinogen.

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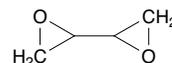
Diepoxybutane

CAS No. 1464-53-5

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as butane diepoxide, butadiene diepoxide, or 1,2:3,4-diepoxybutane



Carcinogenicity

Diepoxybutane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Diepoxybutane caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Dermal application of two forms of 1,2:3,4-diepoxybutane (the D,L and meso forms) caused benign and malignant skin tumors (squamous-cell papilloma and carcinoma) in mice of both sexes (Van Duuren *et al.* 1963, 1965), subcutaneous injection of the D,L racemic mixture caused tumors at the injection site (fibrosarcoma) in female mice and rats (Van Duuren *et al.* 1966), and intraperitoneal injection of L-diepoxybutane caused lung tumors in mice of both sexes (IARC 1976).

Since diepoxybutane was listed in the *Third Annual Report on Carcinogens*, one additional study in rodents has been identified. Inhalation exposure to diepoxybutane caused benign Harderian-gland tumors (adenoma) in mice and increased the incidence of benign or malignant tumors of the nasal cavity (squamous-cell papilloma or carcinoma, sarcoma, or adenocarcinoma) (Henderson *et al.* 1999).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to diepoxybutane.

Properties

Diepoxybutane is an epoxide that is a colorless liquid at room temperature. It is miscible with water and is very flammable and easily ignited by heat or sparks (Akron 2009). Diepoxybutane occurs in several enantiomeric forms, including D,L-1,2:3,4-diepoxybutane, D-1,2:3,4-diepoxybutane, L-1,2:3,4-diepoxybutane, and meso-1,2:3,4-diepoxybutane. Physical and chemical properties of diepoxybutane are listed in the following table (IARC 1976, HSDB 2009).

Property	Information
Molecular weight	86.1 ^a
Specific gravity	0.96 ^a
Melting point	-19°C (meso form) ^a
Boiling point	138°C ^a
Log <i>K</i> _{ow}	-0.28 ^a
Water solubility	1,000 g/L ^b
Vapor pressure	3.9 mm Hg at 20°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Diepoxybutane has been used as a research chemical, as a chemical intermediate, as a curing agent for polymers, as a cross-linking agent for textile fabrics, and to prevent microbial spoilage (IARC 1976, HSDB 2009). It has also been used to synthesize erythritol and pharmaceuticals (HSDB 2009). Because of its cross-linking properties, diepoxybutane is used as a test agent in the diagnosis of Fanconi anemia, which is characterized by chromosomal instability (Auerbach *et al.* 1989).

Production

Diepoxybutane is not produced commercially in the United States (HSDB 2009). In 2009, it was available from eleven suppliers, including four U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of diepoxybutane were found.

Exposure

The primary routes of potential human exposure to diepoxybutane are inhalation and dermal contact. Diepoxybutane is a metabolite of 1,3-butadiene, which is a widely used industrial chemical (Henderson *et al.* 1999). The only environmental releases of diepoxybutane reported in the U.S. Environmental Protection Agency's Toxics Release Inventory between 1988 and 2009 were releases to air of 70 lb in 1998 and 14 lb in 2005 (TRI 2009). Based on its physical and chemical properties, diepoxybutane is not expected to persist in the environment. In air, it is expected to exist in the vapor state and to be degraded by photochemically produced hydroxyl radicals, with a half-life of 16 days. If released to water or soil, it is expected to volatilize; it is not expected to adsorb to soils or sediments or to bioaccumulate in aquatic or terrestrial organisms. Its experimentally determined hydrolysis half-life is 4 to 7 days (HSDB 2009).

Occupational exposure to residues of diepoxybutane may occur during the manufacture of fabrics or polymers or during its use in research (HSDB 2009). Workers and health professionals involved in the formulation, packaging, or administration of pharmaceutical products synthesized from diepoxybutane or in testing for Fanconi anemia may also be exposed.

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 500 lb.

Toxics Release Inventory: Diepoxybutane is subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of diepoxybutane = U085.

Listed as a hazardous constituent of waste.

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Diesel Exhaust Particulates

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Exposure to diesel exhaust particulates is *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies in experimental animals and mechanistic studies.

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of diesel exhaust from studies in humans. Occupational exposure to diesel exhaust particulates was associated with elevated lung-cancer rates in the majority of studies, principally in transportation or construction workers exposed to diesel exhaust (IARC 1989, Cohen and Higgins 1995, Bhatia *et al.* 1998). Meta-analyses by Cohen and Higgins (1995) and Bhatia *et al.* (1998) suggested an overall relative risk of approximately 1.3 to 1.5 for lung cancer; some studies found higher risks in more heavily exposed subgroups. The increased risk was not readily explained by confounding from smoking or exposure to asbestos. However, only some studies used quantitative or semi-quantitative assessments of exposure, and many studies used inadequate measures of exposure.

Since diesel exhaust particulates were listed in the *Ninth Report on Carcinogens*, additional epidemiological studies have been identified. A meta-analysis reported that exposure to diesel exhaust increased the relative risk for lung cancer (Lipsett and Campleman 1999), and additional cohort and case-control studies reported relative risks in the range of 1.2 to 2.21 (Bruske-Hohlfeld *et al.* 2000, Gustavsson *et al.* 2000, Larkin *et al.* 2000, Järholm and Silverman 2003, Kauppinen *et al.* 2003, Garshick *et al.* 2004, 2006, 2008, Laden *et al.* 2006, Parent *et al.* 2007, Neumeyer-Gromen *et al.* 2009). In the majority of studies in which adjustments were made for smoking or other exposures, the increase in risk was not substantially altered; however, as in earlier studies, residual confounding or interactions could not be ruled out. Some studies found higher risk estimates among individuals with higher cumulative exposure (Neumeyer-Gromen *et al.* 2009) or duration of exposure (Laden *et al.* 2006, Garshick *et al.* 2008).

Some studies have also reported increased risks of cancer at other tissue sites, particularly the urinary bladder, but the evidence is generally less consistent than that for lung cancer (Boffetta and Silverman 2001, Boffetta 2004).

Cancer Studies in Experimental Animals

Exposure to diesel exhaust caused tumors in two rodent species, at two different tissue sites, and by several different routes of administration. In numerous studies, inhalation of whole diesel exhaust caused benign or malignant lung tumors (mainly adenoma, squamous-cell carcinoma, or adenocarcinoma) in rats of both sexes (IARC 1989, Brightwell *et al.* 1989, Nikula *et al.* 1995, Heinrich *et al.* 1995). Carcinogenicity appeared to be due to the particulate component of the exhaust, because the filtered vapor phase of exhaust did not cause lung tumors (Brightwell *et al.* 1989, Heinrich *et al.* 1995). Dermal exposure to solvent extracts of diesel exhaust particles caused benign and malignant skin tumors in mice of both sexes, and implantation of wax pellets containing the extracts into the lungs of female rats caused benign and malignant lung tumors (bronchiolar/alveolar adenoma and carcinoma and squamous-cell carcinoma) (IARC 1989).

Studies on Mechanisms of Carcinogenesis

Diesel exhaust contains known mutagens and carcinogens both in the vapor phase and associated with respirable particles (NTP 2000). Diesel exhaust particles are considered likely to account for the human lung cancer findings, because (1) they are almost all small enough to penetrate to the alveolar region in human lungs and (2) mutagenic and carcinogenic chemicals, including polyaromatic hydrocarbons and nitroarenes, have been extracted from these particles with organic solvents or with a lipid component of mammalian lung surfactant. In addition, only diesel exhaust that was not filtered to remove particles caused lung tumors in rats (Brightwell *et al.* 1989, Heinrich *et al.* 1995).

Although exposure to diesel exhaust particulates caused lung cancer in rats, the relevance of this finding for predicting carcinogenicity in humans has been questioned (NTP 2000). Exposure to diesel exhaust particulates caused a spectrum of inflammatory and neoplastic pulmonary responses in rats that are characteristic of responses also seen with other inhaled particles of varying toxicity. These responses apparently are little influenced by the chemical constituents of the particles. The precise bioavailability of chemical mutagens and carcinogens from inhaled diesel particulates is not known; however, DNA adducts were found in the lungs of rats exposed to diesel exhaust particulates (IARC 1989, NTP 2000). Furthermore, more DNA adducts were found in lymphocytes from workers occupationally exposed to diesel exhaust than in those from workers exposed at lower or ambient levels (Hou *et al.* 1995, Nielsen *et al.* 1996). However, diesel exhaust exposure was not quantified in these studies, and exposure to used motor oil may have contributed to the adducts observed in one study.

Properties

Diesel exhaust is a complex mixture of combustion products of diesel fuel, and the exact composition of the mixture depends on the nature of the engine, operating conditions, lubricating oil, additives, emission control system, and fuel composition (Obert 1973, Ullman 1989). Diesel engines typically are classified by their service requirements, and the operating conditions for light- and heavy-duty diesel engines differ with respect to engine speed, expected load, fuel composition, and engine emission controls. Light-duty vehicles, such as automobiles and light trucks, typically operate at higher speeds than do heavy-duty vehicles, such as trucks. Depending on operating con-

ditions, fuel composition, and engine-control technology, light- and heavy-duty diesel engines, respectively, can emit 50 to 80 times and 100 to 200 times as much particulate mass as typical catalyst-equipped gasoline engines (McClellan 1986).

Most diesel exhaust particles have aerodynamic diameters falling within a range of 0.1 to 0.25 μm (Groblicki 1979, Dolan *et al.* 1980, NCR 1982, Williams 1982). The particle size distribution of diesel exhaust is bimodal, with a nuclei mode of 0.0075 to 0.042 μm (for particles formed by nucleation) and an accumulation mode of 0.042 to 1.0 μm (for particles formed by agglomeration of nuclei particles) (Baumgard and Johnson 1996). Approximately 92% of the particles emitted from diesel engines are less than 1.0 μm in diameter (CARB 1997).

Diesel emissions consist of a nonpolar fraction (57%), a moderately polar fraction (9%), and a polar fraction (32%) (Schuetzle and Perez 1983, Schuetzle *et al.* 1985); the remainder is unrecoverable. The inorganic fraction of the particulate emissions consists primarily of small elemental carbon particles, ranging from 0.01 to 0.08 μm in diameter. Organic and elemental carbon account for approximately 80% of the total particulate matter mass. The remaining 20% is composed of sulfate (mainly sulfuric acid) (Pierson and Brachaczek 1983) and some inorganic additives and components of fuel and motor oil. In general, the organic compounds identified in diesel exhaust emissions contain hydrocarbons, such as alkanes and alkenes, hydrocarbon derivatives, aldehydes, polyaromatic hydrocarbons (PAHs), PAH derivatives, multifunctional derivatives of PAHs, heterocyclic compounds, heterocyclic derivatives, and multifunctional derivatives of heterocyclic compounds (Schuetzle 1988).

Because of their large surface area, diesel exhaust particulates can adsorb relatively large amounts of organic material coming from unburned fuel, lubricating oil, and pyrosynthesis during fuel combustion. A variety of mutagens and carcinogens, such as PAHs and nitro-PAHs, are adsorbed by the particulates (NCR 1982, Tokiwa and Ohnishi 1986, IPCS 1996). The organic-extractable fraction of diesel exhaust particulates is typically in the 20% to 30% range, but it may be as high as 90% (Williams *et al.* 1989), depending upon vehicle type and operating conditions. In general, incomplete combustion in diesel engines operating under low-load conditions produces relatively low particle concentrations and a higher proportion of organic material associated with the particles (Dutcher *et al.* 1984). Particulate matter produced at low exhaust-gas temperatures has more adsorbed soluble organics than does particulate matter produced at high exhaust-gas temperatures (Kishi *et al.* 1992).

Use

Diesel exhaust particulates have no known uses.

Production

Internal combustion engines have been used in cars, trucks, locomotives, and other motorized machinery for about 100 years (IARC 1989). Diesel exhaust has three major groups of sources: mobile sources (on-road vehicles and other mobile sources), stationary area sources (e.g., oil- and gas-production facilities, stationary engines, repair yards, and shipyards), and stationary point sources (e.g., chemical-manufacturing facilities and electric utilities). As discussed above, the composition and quantity of the emissions depend mainly on the type and condition of the engine, fuel composition and additives, operating conditions, and emission-control devices.

Diesel engines operate with excess air (~25 to 30 parts air to 1 part fuel) (Lassiter and Milby 1978). The gas-phase fraction of emissions is composed primarily of typical combustion gases such as nitrogen, oxygen, carbon dioxide, and water vapor. As a result of incom-

plete combustion, the gaseous fraction also contains pollutants such as carbon monoxide, sulfur oxides, nitrogen oxides, volatile hydrocarbons, and low-molecular-weight PAHs and their derivatives. The total particulate emission concentration from light-duty diesel engines is much smaller than that from heavy-duty diesel engines. In general, newer heavy-duty trucks emit diesel particulates at a rate 20 times that of catalyst-equipped gasoline-fueled vehicles (IPCS 1996).

Exposure

Occupational exposure to diesel exhaust particulates has been studied among railroad workers, mine workers (who use diesel-powered equipment), bus-garage workers, trucking-company workers, forklift truck operators, firefighters, lumberjacks, toll-booth and parking-garage attendants, and workers in many occupations involved in servicing or handling automobiles (e.g., car mechanics and professional drivers). The National Institute for Occupational Safety and Health estimated that 1.35 million workers were occupationally exposed to diesel exhaust particulates in 80,000 U.S. workplaces (MMWR 1989).

Railroad workers' potential for exposure has increased since 1959, when almost all of the U.S. railroad system (95%) converted to diesel engines. In studies conducted between 1996 and 2002, occupational exposure to elemental carbon was reported to be 4 to 20 $\mu\text{g}/\text{m}^3$ for train crews and 3 to 39 $\mu\text{g}/\text{m}^3$ for maintenance crews (Pronk 2009). Exposure to respirable particulate matter ranged from 17 $\mu\text{g}/\text{m}^3$ for clerks to 134 $\mu\text{g}/\text{m}^3$ for locomotive shop workers (Woskie *et al.* 1988). More recently, the U.S. Environmental Protection Agency reported that exposure of locomotive workers to respirable particulate matter ranged from 39 to 191 $\mu\text{g}/\text{m}^3$ (EPA 2002). In a railway repair facility in England, mean personal exposure to respirable particulate matter was 250 $\mu\text{g}/\text{m}^3$, and the concentration in ambient air was 163 $\mu\text{g}/\text{m}^3$ (Groves and Cain 2000).

Diesel engines have been, and continue to be, commonly used in U.S. mines since their first introduction in the early 1950s. Exposure occurs from activities that use diesel-fueled heavy machinery, such as blasting. From 1997 to 2004, occupational exposure to respirable elemental carbon in U.S. underground mining operations ranged from 148 to 637 $\mu\text{g}/\text{m}^3$ (Pronk *et al.* 2009). In surface mining operations, concentrations of respirable or submicron elemental carbon ranged from 13 to 23 $\mu\text{g}/\text{m}^3$. In enclosed spaces of mines, diesel exhaust particulate concentrations were up to 1,280 $\mu\text{g}/\text{m}^3$ (EPA 2002).

Exposure of mechanics in bus garages and truck terminals to respirable elemental carbon ranged from 20 to 40 $\mu\text{g}/\text{m}^3$ (Pronk 2009). Levels of diesel exhaust emissions were elevated at a bus garage during peak hours of bus activity (i.e., starting of buses) but rapidly returned to normal in 10 to 15 minutes (Pryor 1983). In another study, mean personal exposure to respirable particulate matter was 267 $\mu\text{g}/\text{m}^3$, and the mean concentration in ambient air was 211 $\mu\text{g}/\text{m}^3$ (Groves and Cain 2000). At a New York City bus stop, respirable particulate matter from diesel exhaust was measured at 46.7 $\mu\text{g}/\text{m}^3$ and was estimated to constitute 53% of the particulate matter in ambient air at that site (EPA 2002).

Exposure of truck drivers to elemental carbon in submicron particulate matter generally ranged from 1 to 10 $\mu\text{g}/\text{m}^3$ (Pronk *et al.* 2009). Temperature was an important factor, with higher exposures occurring at higher temperatures (Zaebst *et al.* 1991). This study found no discernible difference between truckers' exposure levels (3.8 $\mu\text{g}/\text{m}^3$) and highway background concentrations (2.5 $\mu\text{g}/\text{m}^3$), indicating that the highway environment, rather than the truck itself, was the source of the truck drivers' exposure. Exposure of mechanics to elemental carbon in truck terminals ranged from 20 to 40 $\mu\text{g}/\text{m}^3$.

Exposure of firefighters in fire stations to inhalable elemental carbon ranged from 10 to 40 $\mu\text{g}/\text{m}^3$ (Pronk 2009). Diesel fire trucks idling in a fire station can spread exhaust throughout the entire station (NJDHSS 2001). Firefighters in New York, Boston, and Los Angeles were studied to determine exposure to diesel exhaust particulates (Froines *et al.* 1987). Total exposure to airborne particles was measured with personal air samplers, and sampling was performed only when firefighters were in the fire stations. For the three cities, total airborne particulate exposure had a time-weighted average ranging from below 100 $\mu\text{g}/\text{m}^3$ to 480 $\mu\text{g}/\text{m}^3$. For a "worst-case" scenario, the mean concentrations were as high as 748 $\mu\text{g}/\text{m}^3$. The authors noted that these were busy fire stations in large metropolitan areas. Other factors, such as smoking, building design, age and maintenance of vehicles, activities of the firefighters, and timing of runs, also affected the results.

Occupational exposure to diesel exhaust from off-road vehicles was reported for construction and forklift operators in several settings (Pronk *et al.* 2009). Exposure to elemental carbon ranged from 132 to 314 $\mu\text{g}/\text{m}^3$ for tunnel construction, compared with only 4 to 13 $\mu\text{g}/\text{m}^3$ for outdoor highway construction. Exposure to inhalable or respirable elemental carbon was 4 to 122 $\mu\text{g}/\text{m}^3$ for dockworkers, including forklift operators; 6 to 49 $\mu\text{g}/\text{m}^3$ for workers loading and unloading ships; and 11 $\mu\text{g}/\text{m}^3$ for airline personnel in baggage and screening. Three studies reviewed by the International Agency for Research on Cancer found that toll-booth workers had elevated levels of exposure to diesel exhaust particulates. In many of these studies, however, it was difficult to differentiate between gasoline exhaust and diesel exhaust (IARC 1989).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

Mine Safety and Health Administration

Standards have been developed for diesel exhaust monitoring and exposure mitigation in underground coal mines.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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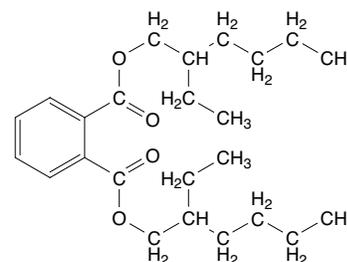
Di(2-ethylhexyl) Phthalate

CAS No. 117-81-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as DEHP, diethylhexyl phthalate, or dioctyl phthalate



Carcinogenicity

Di(2-ethylhexyl) phthalate (DEHP) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to DEHP caused benign and/or malignant liver tumors (hepatocellular adenoma and/or carcinoma) in mice and rats of both sexes, and the tumor incidences showed significant dose-related trends in both species (NTP 1982).

Since DEHP was listed in the *Third Annual Report on Carcinogens*, additional studies in rodents have been identified, which confirmed that DEHP caused liver tumors in rats and mice. DEHP also caused liver tumors in PPAR α -null mice, which lack the peroxisome proliferator-activated receptor α (which has been proposed to be involved in DEHP-induced tumorigenesis) (Ito *et al.* 2007). In addition, dietary exposure to DEHP caused benign testicular tumors (Leydig-cell tumors) (Voss *et al.* 2005) and benign pancreatic tumors (acinar-cell and islet-cell adenoma) in male rats (Rao *et al.* 1990, David *et al.* 2000). Initiation-promotion studies in two strains of mice provided evidence that DEHP acted as a promoter of liver tumors (IARC 2000).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to DEHP (IARC 1982).

Properties

DEHP is a phthalate ester that exists as a colorless oily liquid with a slight odor. It is slightly soluble in water and carbon tetrachloride, miscible with mineral oil and hexane, and soluble in blood and body fluids containing lipoproteins. When heated to decomposition, it emits acrid smoke. DEHP is incompatible with nitrates, strong oxidizers, acids, and alkalis (HSDB 2010). DEHP is available in the United States in a variety of technical grades. Typical product specifications include 99.0% to 99.6% minimal ester content, 0.1% maximal moisture content, and 0.007% to 0.01% acidity (as acetic acid or phthalic acid) (IARC 2000). Physical and chemical properties of DEHP are listed in the following table.

Property	Information
Molecular weight	390.6
Specific gravity	0.986 at 20°C/20°C
Melting point	-55°C
Boiling point	384°C
Log K_{ow}	7.6
Water solubility	0.27 mg/L at 25°C
Vapor pressure	1.42×10^{-7} mm Hg at 25°C

Source: HSDB 2010.

Use

About 95% of DEHP produced is used as a plasticizer in polyvinyl chloride (PVC) resins for fabricating flexible vinyl products (ATSDR 2002). Products typically contain from 1% to 40% DEHP; however, Tickner *et al.* (2001) reported that DEHP levels in PVC medical tubing may be as high as 80%. Plasticized PVC has been used in many consumer items and building products, such as tablecloths, shower curtains, furniture and automobile upholstery, imitation leather, garden hoses, floor tiles, swimming-pool liners, sheathing for wire and cable, rainwear, shoes, toys, dolls, baby pants, food packaging materials, tubing used in commercial milking equipment, and weather stripping (IARC 2000, ATSDR 2002, Bizzari *et al.* 2007). DEHP is also used in medical devices (blood and intravenous solution bags, catheters, tubing for dialysis and parenteral solutions, oxygen masks, and urine and colostomy bags) and in disposable surgical gloves. It has been used as a plasticizer in non-PVC materials, including polyvinyl butyral, natural and synthetic rubber, chlorinated rubber, ethyl cellulose, and nitrocellulose. In 2005, the breakdown of U.S. consumption of DEHP as a plasticizer was reported to be 40% for medical devices, 30% for consumer goods, and 30% for construction-related applications (Bizzari *et al.* 2007).

Non-plasticizer uses of DEHP include its use in dielectric fluids for electric capacitors, as an acaricide in orchards, as an inert ingredient in pesticides, in cosmetic products, as a vacuum-pump oil, to detect leaks in respirators, and in testing air-filtration systems. However, some of these applications are believed to be no longer in use or were never carried out on a commercial scale (IARC 2000, ATSDR 2002).

Historically, DEHP constituted about 50% of all the phthalate ester plasticizers used (IPCS 1992). However, the use of DEHP in some products has diminished because of health concerns and regulatory limitations on its use (ATSDR 2002, HCWH 2002). Furthermore, DEHP is being replaced by linear phthalates and other plastomers in many other applications, because of their superior performance and low toxicity (ATSDR 2002). In the United States, DEHP constituted roughly 10% of all plasticizers consumed in 2005; this was the smallest percentage of the total DEHP demand among the major world regions (compared with 18% in Western Europe, 52% in Japan, and 62.4% in "Other Asia").

Production

DEHP was first produced in the United States in 1939. Annual U.S. production remained fairly steady from 1975 to 2003, ranging from a peak of 180,000 metric tons (397 million pounds) in 1976 to a low of 109,000 metric tons (240 million pounds) in 1993. Total U.S. phthalate production in 2005 (the last year for which production data were available) was 88,000 metric tons (194 million pounds), accounting for 14.5% of total phthalate plasticizer production (Bizzari *et al.* 2007). In 2010, DEHP was produced by two U.S. companies (SRI 2010) and was available from 109 suppliers worldwide, including 45 U.S. suppliers (ChemSources 2010). In 2009, U.S. imports and exports of dioctyl orthophthalates totaled 6,896 metric tons (15.2 million pounds) and 3,630 metric tons (8 million pounds), respectively (USITC 2010).

Exposure

The primary routes of potential human exposure to DEHP are ingestion, inhalation, and through medical procedures; exposure levels are highest for medical procedures (ATSDR 2002, NTP 2006). Dermal absorption is another potential exposure route; however, dermal absorption of DEHP *in vitro* is low (IARC 2000).

Individuals receiving treatment with medical products containing DEHP are at risk for high DEHP exposure; exposure of newborn infants is of particular concern. For both adults and neonates, the highest estimated daily exposure levels were for blood transfusion, at 22.6 mg/kg of body weight for neonatal exchange transfusion and 8.5 mg/kg for transfusion in adult trauma patients. The U.S. Food and Drug Administration expressed special concern about aggregate exposure from repeated medical procedures, which often occurs in neonatal intensive-care settings. Other medical procedures that can result in DEHP exposure include hemodialysis, transfusion of platelets or plasma, pheresis, nasogastric feeding, and respirator use (FDA 2001). Long-term use of some procedures can result in significant total DEHP exposure. DEHP has been measured in large-volume parenteral formulations (i.e., fluids, nutrients, and electrolytes) and in whole blood and plasma stored in flexible-PVC bags (FDA 2001, ATSDR 2002). DEHP was found in condensate from respirator water traps at concentrations of up to 4,100 mg/L (IARC 2000).

Exposure to DEHP or its metabolites may occur in utero. DEHP and its major metabolite mono(2-ethylhexyl) phthalate (MEHP) were detected in cord blood collected from 84 newborns in Italy (Latini *et al.* 2003b), and MEHP was detected in 24% of 54 amniotic-fluid samples collected by amniocentesis (Silva *et al.* 2004).

A substantial fraction of the U.S. general population is exposed to measurable levels of DEHP because of its widespread use in consumer products and its presence in foods, beverages, and the environment. For the general population, the most important route of exposure is ingestion. DEHP has been found at low levels in packaged food as a result of its use as a plasticizer in products that contact food during its manufacture or storage (ATSDR 2002). DEHP has been detected in fish and other seafood, cheese, margarine, eggs, meat, cereal, baby food, milk, and infant formula. Because DEHP is lipophilic, higher levels are expected in fattier foods than in less fatty foods. In colostrum or milk from 17 healthy mothers, DEHP was detected in 16 of 17 samples and MEHP in 2 of 17 samples (Latini *et al.* 2003a). It has been estimated that more than 90% of daily intake of DEHP by non-infants is from dietary intake of food, water, and other beverages (Clark *et al.* 2003b). Daily exposure of adults in the general population was estimated to range from 1 to 30 µg/kg of body weight (0.001 to 0.03 mg/kg) (NTP 2006). Exposure may be several times as high in infants and toddlers, as a result of non-dietary mouthing behaviors (e.g., chewing on soft-PVC plastic toys and ingesting household dust), with ingestion of household dust accounting for about half of

total DEHP intake for infants (ATSDR 2002, Clark *et al.* 2003b). The concentration of DEHP in house dust was associated with the use of PVC-based flooring and wall coverings in the home; however, DEHP was also found in buildings that did not use PVC flooring or vinyl wall coverings (Bornehag *et al.* 2005). Based on limited data, concentrations of DEHP in house dust are expected to range from a few hundred to several thousand parts per million (IARC 2000, ATSDR 2002, Clark *et al.* 2003a, Rudel *et al.* 2003). Soft-PVC children's toys may contain DEHP, and children may ingest DEHP by sucking or chewing on the toys. DEHP was the most common plasticizer used in pacifiers and teethers until the early 1980s, when manufacturers voluntarily agreed to eliminate its intentional addition (ATSDR 2002). However, a study published in 2005 found that 12 of 18 such children's products contained DEHP at levels ranging from 20 to 840 ppm, including a teething ring that contained 410 ppm (Hileman 2005).

DEHP is considered a ubiquitous environmental contaminant and has been measured in outdoor and indoor air, water, sediment, and soil (IARC 2000, ATSDR 2002). DEHP is released to the environment from industrial facilities and waste-treatment plants. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of DEHP declined steadily from 4.9 million pounds in 1988 to 1.5 million pounds in 1997 and have since leveled off, with only minor variation from year to year. In 2008, releases of DEHP totaled around 960,000 lb (TRI 2010). In air, DEHP is expected to react with hydroxyl radicals, with an estimated half-life of about 6 hours. However, the expected adsorption of most DEHP to atmospheric particulates will decrease the reaction with hydroxyl radicals, resulting in a potentially longer atmospheric half-life. DEHP is readily removed from the atmosphere by rain or snow (ATSDR 2002).

DEHP in indoor air is due primarily to volatilization from consumer products and building materials that contain DEHP. In general, concentrations are expected to be higher in indoor air than in outdoor ambient air (ATSDR 2002). DEHP has also been measured at high air concentrations in cars. Some studies have suggested that because of DEHP's tendency to adsorb to airborne particulates, levels estimated based only on gas-phase measurements might underestimate total air levels. It was suggested that exposure to DEHP from indoor air may increase by a factor of up to three when particulate-matter contributions are accounted for (Øie *et al.* 1997).

DEHP has been detected in drinking water, surface water, ground-water, rainwater, and seawater, generally in the low parts-per-billion range. In water, DEHP is expected mainly to adsorb to suspended particulates; its evaporation from water is expected to be negligible (ATSDR 2002). However, its degradative half-life has been estimated to be roughly 10 hours in river water and 2 weeks in river sediment (Yuwatini *et al.* 2006). The main sources of DEHP released to land and soil are disposal of industrial and municipal waste to landfills and land application of DEHP-containing sludges (e.g., industrial or sewage sludges). Disposal of products containing flexible PVC, such as food wraps, may be a source of DEHP in municipal waste (IARC 2000). DEHP adsorbs strongly to soil, thus limiting losses from volatilization or leaching; however, co-disposal with common organic solvents could increase its solubility and its mobility in soil.

Air concentrations of DEHP in occupational settings (i.e., industrial production) may be significantly higher than general indoor levels. Occupational exposure to DEHP occurs primarily among workers involved in the manufacture and processing of DEHP and flexible-PVC plastics and plastic products, with inhalation of aerosols or mists the major route of exposure (IARC 2000, ATSDR 2002). DEHP is easily released into air at typical PVC-processing temperatures (Vainiotalo and Pfaffli 1990). However, few data are available on occupational exposure to DEHP. Air exposure levels of DEHP were reported to

range from below the limit of detection to 4.1 mg/m³ across various processes at a U.S. production facility. Higher urinary levels of DEHP, its metabolites, and total phthalates have been measured in DEHP-exposed workers than in non-exposed workers and in post-shift samples than in pre-shift samples (IARC 2000).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that pacifiers, rattles, and teethers shall not intentionally contain DEHP. It is unlawful for any person to manufacture for sale, offer for sale, distribute in commerce, or import into the United States any children's toy or child-care article that contains DEHP at concentrations of more than 0.1%.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of DEHP is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Phthalate esters are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 1.2 µg/L; based on fish or shellfish consumption only = 2.2 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of DEHP = U028.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.006 mg/L.

Food and Drug Administration (FDA)

Limitations on the use of DEHP in basic components of single and repeated use food contact surfaces are prescribed in 21 CFR 177.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 5 mg/m³.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 5,000 mg/m³.

Recommended exposure limit (time-weighted-average workday) = 5 mg/m³.

Short-term exposure limit (STEL) = 10 mg/m³.

Listed as a potential occupational carcinogen.

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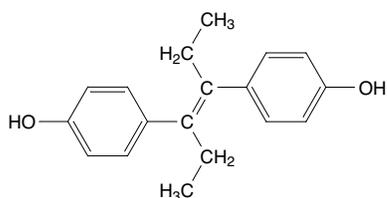
Diethylstilbestrol

CAS No. 56-53-1

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as DES, diethylstilboestrol, or stilboestrol



Carcinogenicity

Diethylstilbestrol is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

The strongest evidence for carcinogenicity comes from epidemiological studies of women exposed to diethylstilbestrol *in utero* (“diethylstilbestrol daughters”), which found that diethylstilbestrol caused clear-cell adenocarcinoma, a rare cancer of the vagina and cervix. This type of cancer, which typically develops in elderly women, developed in diethylstilbestrol daughters between the ages of 10 and 30 years. Most (though not all) case-control studies found that *in utero* exposure to diethylstilbestrol also increased the risk of testicular cancer in males (“diethylstilbestrol sons”). Several follow-up studies (including cohort studies and randomized clinical trials) found that women who took diethylstilbestrol at high doses during pregnancy were at increased risk for breast cancer. Some studies suggest that diethylstilbestrol-induced breast cancer may have a long latency period (15 to 20 years), but the evidence is inconclusive. As has been found for other estrogens, diethylstilbestrol taken to relieve the symptoms of menopause increases the risk of endometrial cancer (IARC 1974, 1979, 1987).

Since diethylstilbestrol was reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, additional studies on diethylstilbestrol daughters and sons have been published. A study of a large cohort of diethylstilbestrol daughters first identified in the mid 1970s confirmed a 40-fold increase in the risk of clear-cell adenocarcinoma of the vagina or cervix and estimated a cumulative incidence rate of 1.5 per 1,000 exposed women (Hatch *et al.* 1998). The evidence for increased risk of breast cancer in diethylstilbestrol daughters is inconclusive because of the young age of the cohort (Hatch *et al.* 1998, Palmer *et al.* 2002). Another cohort study reported an increased risk of testicular cancer among diethylstilbestrol sons, supporting the findings from earlier case-control studies; however, this result was not statistically significant (Strohsnitter *et al.* 2001).

Cancer Studies in Experimental Animals

Diethylstilbestrol caused tumors in several animal species, by several different routes of exposure, and at several different tissue sites (primarily estrogen-sensitive organs and tissues). Diethylstilbestrol has been tested by oral administration (mice and rats), local application (mice), subcutaneous implantation or injection (frogs, mice, rats, hamsters, dogs, and monkeys), prenatal exposure (mice, hamsters, and monkeys), and neonatal exposure (mice and rats).

Prenatal exposure to diethylstilbestrol caused benign cervical and vaginal tumors (epidermoid tumors) in female mice, benign and malignant cervical and vaginal tumors (polyps, squamous-cell papilloma, and myosarcoma) in female hamsters, and benign and malignant testicular tumors (granuloma, adenoma, and leiomyosarcoma) in male hamsters. Prenatal exposure also caused uterine cancer (adenocarcinoma) in female mice and hamsters, benign ovarian tumors (cystadenoma and granulosa-cell tumors) in female mice, and benign lung tumors (papillary adenoma) in mice of both sexes. Prenatal exposure did not cause tumors in monkeys observed for up to six years after birth. Mice developed cervical and vaginal tumors after receiving a single subcutaneous injection of diethylstilbestrol on the first day of life, and male rats developed cancer of the reproductive tract (squamous-cell carcinoma) after receiving daily subcutaneous injections for the first month of life.

Diethylstilbestrol also caused cancer in experimental animals exposed as adults. When administered orally, diethylstilbestrol caused

cancer of the mammary gland (carcinoma and adenocarcinoma) in mice of both sexes and benign mammary-gland tumors (fibroadenoma) in rats of both sexes. In addition, cancer of the cervix and uterus (adenocarcinoma), vagina (squamous-cell carcinoma), and bone (osteosarcoma) occurred in mice, and benign and malignant pituitary-gland and liver tumors (hepatocellular tumors and heman-gioendothelioma) occurred in rats. Intravaginal application of diethylstilbestrol to mice caused cancer of the vagina and cervix (epidermoid carcinoma). Subcutaneous injections or implants of diethylstilbestrol in mice increased the incidences of leukemia and benign or malignant tumors of the testis (interstitial-cell tumors), lymphoid tissue, mammary gland (carcinoma), cervix, vagina, and ovary (cystadenoma). Subcutaneous administration to rats increased the incidences of benign or malignant tumors of the mammary gland (fibroadenoma, carcinoma, or adenocarcinoma), bladder (carcinoma), and adrenal gland. Subcutaneously administered diethylstilbestrol also increased the incidences of kidney cancer (carcinoma) in male hamsters, benign or malignant ovarian tumors (papillary adenoma or carcinoma) in dogs, and uterine tumors (mesothelioma) in squirrel monkeys. Subcutaneous injection of diethylstilbestrol dipropionate caused tumors of the liver and the hematopoietic system (organs and tissues involved in production of blood) in male and female frogs and benign pituitary-gland tumors in rats (IARC 1974, 1979).

Since diethylstilbestrol was listed in the *First Annual Report on Carcinogens*, multigenerational studies in mice and several additional prenatal-exposure studies in rats have been published. In the multi-generational studies, mice were exposed to diethylstilbestrol *in utero*, either during the period of major organogenesis, or just before birth, or on the first five days of life. Female mice from each exposure regimen (the F₁ generation) were raised to maturity and bred with unexposed male mice. Offspring of these mice (the F₂ generation) had increased incidences of reproductive-tract tumors. Females developed uterine cancer (adenocarcinoma), and males developed cancer of the rete testis (the network of sperm-carrying tubules) and benign and malignant seminal-vesicle tumors (papilloma, carcinosarcoma, and sarcoma) (Newbold *et al.* 1998, 2000). Prenatal exposure to diethylstilbestrol also caused uterine cancer (adenocarcinoma) in Donryu rats (a carcinogen-sensitive strain with an increased estrogen-to-progesterone ratio) (Kitamura *et al.* 1999).

Properties

Diethylstilbestrol is a synthetic nonsteroidal estrogen that is an odorless white crystalline powder at room temperature. It is practically insoluble in water and soluble in alcohol, ether, chloroform, fatty oils, dilute hydroxides, acetone, dioxane, ethyl acetate, methanol, and vegetable oils. The *trans*-isomer is used for commercial purposes and is stable in the environment. The *cis*-isomer is not stable and tends to convert to the *trans* form (IARC 1979). Diethylstilbestrol dipropionate is an ester of diethylstilbestrol with propionic acid that is soluble in organic solvents and vegetable oils (O'Neil *et al.* 2006). Physical and chemical properties of diethylstilbestrol are listed in the following table.

Property	Information
Molecular weight	268.4
Melting point	169°C to 172°C
Log <i>K</i> _{ow}	5.07
Water solubility	0.012 g/L at 25°C

Source: HSDB 2009.

Use

Diethylstilbestrol was the first synthetic estrogen, originally synthesized in 1938. It was widely prescribed in the United States from

the early 1940s until 1971, primarily as a treatment to prevent miscarriages or premature deliveries. The U.S. Food and Drug Administration issued a drug bulletin in 1971 advising physicians to stop prescribing diethylstilbestrol to pregnant women because of its link to a rare vaginal cancer (clear-cell adenocarcinoma) in diethylstilbestrol daughters (CDC 2003). Other uses in human medicine continued at least through the 1970s and in some cases into the early 1980s. These uses included hormone-replacement therapy, control of menstrual disorders, relief or prevention of postpartum breast engorgement, palliative therapy for cancer of the prostate in men and breast cancer in postmenopausal women, and as a postcoital contraceptive. In 1978, the FDA withdrew approval of any estrogen-containing drug product (including diethylstilbestrol) for the suppression of postpartum breast engorgement (FDA 1998). Diethylstilbestrol sometimes was given in combination with androgens, vitamins, and antibiotics (IARC 1974, 1979). Its use in the treatment of advanced prostate cancer fell out of favor because of its cardiovascular toxicity, the emergence of safer agents, and manufacturers' economic considerations (Malkowicz 2001). Nevertheless, diethylstilbestrol continues to be used in clinical trials for treatment of prostate and breast cancer (Smith *et al.* 1998, Peethambaram *et al.* 1999) and in biochemical research.

Diethylstilbestrol has also been used in veterinary medicine and as a growth promoter (as a feed supplement or subcutaneous implant) in cattle, sheep, and poultry (IARC 1979). Its use as a growth promoter was banned in 1979 (Raun and Preston 2002).

Production

U.S. production of diethylstilbestrol was first reported in 1941, as 227 kg (500 lb), and last reported in 1952, as 1,800 kg (3,970 lb) (IARC 1974). In 1972, 454 kg (1,000 lb) of diethylstilbestrol diphosphate (an ester form) was produced (HSDB 2009). From the early 1940s to the early 1970s, three to five U.S. companies produced diethylstilbestrol; by 1976, there was one U.S. producer (IARC 1974, 1979). Diethylstilbestrol is no longer manufactured by U.S. pharmaceutical companies (CDC 2004), but 17 U.S. suppliers of diethylstilbestrol were identified in 2009 (ChemSources 2009). Annual U.S. imports of diethylstilbestrol ranged from about 3,000 to 7,800 kg (6,700 to 17,000 lb) in the 1970s, but had dropped to 130 kg (290 lb) by 1982 (IARC 1974, 1979, HSDB 2009). No data on U.S. exports of diethylstilbestrol were found.

Exposure

Most current exposure to diethylstilbestrol is through its oral administration as a drug in clinical trials for the treatment of prostate and breast cancer. Exposure also occurred in the past through the use of diethylstilbestrol to prevent miscarriages, as hormone replacement therapy, to treat prostate cancer, and in other medical therapies. It has been estimated that between 5 million and 10 million Americans received diethylstilbestrol during pregnancy or were exposed to the drug *in utero* (NIH 1999). In one large cohort of diethylstilbestrol daughters, the median total doses administered to their mothers at five study sites ranged from 1,625 to 10,424 mg (Giusti *et al.* 1995). Many different forms of diethylstilbestrol, including oral tablets (0.1, 0.25, 0.5, 1, and 5 mg), injectable solutions (0.2, 0.5, 1, and 5 mg/mL), and a vaginal suppository (0.1 and 0.5 mg) were approved by the FDA (FDA 2009). Diethylstilbestrol diphosphate also was available as oral tablets (50 mg) and as an injectable solution (250 mg/50 mL).

Diethylstilbestrol residues were detected in beef and sheep livers in 1972 and 1973. When diethylstilbestrol was used as a growth promoter for sheep and cattle, people could have been exposed to it at concentrations of up to 10 ppb in beef and mutton.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,492 workers, including 934 women, potentially were exposed to diethylstilbestrol during its manufacture or during product formulation (NIOSH 1990). The concentration of diethylstilbestrol in ambient-air samples from plants that manufactured diethylstilbestrol ranged from 0.02 to 24 $\mu\text{g}/\text{m}^3$ (IARC 1979).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of diethylstilbestrol = U089.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

All oral and parenteral drug products containing greater than 25 mg per unit dose of diethylstilbestrol were removed from the market because they were found to be unsafe or not effective, and they may not be compounded.

Diethylstilbestrol is prohibited from extralabel use in food-producing animals.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

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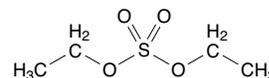
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Diethyl Sulfate

CAS No. 64-67-5

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Diethyl sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Diethyl sulfate caused tumors in rats at several different tissue sites and by several different routes of exposure. Administration of diethyl sulfate by stomach tube caused benign or malignant forestomach tumors (papilloma or squamous-cell carcinoma) in rats of unspecified sex. Prenatal exposure to diethyl sulfate caused cancer of the nervous system, and cancer at the injection site (malignant sarcoma) was observed after subcutaneous injection (IARC 1974, 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to diethyl sulfate. Exposure to diethyl sulfate occurs mainly during ethanol production. In most studies of ethanol production workers, diethyl sulfate was not measured, making it difficult to evaluate the contribution of diethyl sulfate to cancer risk. A retrospective cohort study of morbidity and mortality among 355 ethanol and isopropanol production workers found a significant excess of laryngeal cancer (4 deaths) (Lynch *et al.* (1979). When the cohort was expanded to include maintenance workers and supervisors (a total of 740 workers and 7 deaths), the excess of laryngeal cancer was smaller but still statistically significant. Within the expanded cohort, a nested case-control study of 50 cases of throat cancer found a relationship between cancer and the level of exposure to sulfuric acid; however, the increased risk persisted after workers in the ethanol and isopropanol units were excluded (Soskolne *et al.* 1984). A nested case-

control study of 17 benign brain tumors (glioma) among workers at a petrochemical plant found the risk of brain cancer to be associated with estimated exposure to diethyl sulfate (Leffingwell *et al.* 1983); however, no increased risk was found in an overlapping study of 21 cases (including the 17 cases of the Leffingwell study) with a different series of controls (Austin and Schnatter 1983).

Properties

Diethyl sulfate is the diethyl ester of sulfuric acid and exists at room temperature as a colorless oily liquid with a faint peppermint odor. It is slightly soluble in water, but miscible with alcohol, diethyl ether, and most polar solvents. Diethyl sulfate readily decomposes in hot water to ethyl hydrogen sulfate and ethyl alcohol (IARC 1974, 1992). Physical and chemical properties of diethyl sulfate are listed in the following table.

Property	Information
Molecular weight	154.2
Density	1.17 g/cm ³ at 25°C
Melting point	-25°C
Boiling point	210°C with decomposition
Log <i>K</i> _{ow}	1.14
Water solubility	7.0 g/L at 20°C
Vapor pressure	0.212 mm Hg at 25°C
Vapor density relative to air	5.31

Source: HSDB 2009.

Use

The primary use of diethyl sulfate is as a chemical intermediate (ethylating agent) in synthesis of ethyl derivatives of phenols, amines, and thiols; as an accelerator in the sulfation of ethylene; and in some sulfonation processes. It is used to manufacture dyes, pigments, carbonless paper, and textiles. It is an intermediate in the indirect hydration (strong acid) process for the preparation of synthetic ethanol from ethylene. Smaller quantities are used in household products, cosmetics, agricultural chemicals, pharmaceuticals, and laboratory reagents (IARC 1992, 1999, HSDB 2009). In 1966, it was used as a mutagen to create the Luther variety of barley (IARC 1974).

Production

Diethyl sulfate has been produced commercially in the United States since at least the 1920s (IARC 1974). In 2009, diethyl sulfate was produced by two manufacturers in East Asia, and four each in the United States and India (SRI 2009) and was available from 28 suppliers, including 13 U.S. suppliers (ChemSources 2009). No data on U.S. exports or imports specifically of diethyl sulfate were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of diethyl sulfate totaled 1 million to 10 million pounds between 1986 and 2006, except in 1994, when the quantity increased to 10 million to 50 million pounds (EPA 2004, 2009).

Exposure

The routes of potential human exposure to diethyl sulfate are inhalation, ingestion, and dermal contact during its production and use. Diethyl sulfate can be released to the environment during its production and use in the synthesis of various intermediates and products (IARC 1992, HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of diethyl sulfate since 1988 have ranged from a high of over 38,000 lb in 1999 (including 34,500 lb sent to an off-site landfill) to a low of 4,000 lb in 1991. Most of the releases from 1988 to 2007 (≥ 93%) were to air, and the remainder were to off-site landfills. In 2007, seven facilities released 5,346 lb of diethyl

sulfate, all to air (TRI 2009). If released to air, diethyl sulfate will exist as a vapor, with a half-life of 9 days by reaction with photochemically produced hydroxyl radicals and a half-life of less than 1 day by hydrolysis. In soil and water, diethyl sulfate will hydrolyze rapidly, with a half-life in water of 1.7 hours. Because of its sensitivity to hydrolysis, the processes of volatilization, adsorption to soil and sediment, biodegradation, and bioaccumulation are not expected to be significant. Hydrolysis of diethyl sulfate produces monoethyl sulfate and ethanol (IARC 1992).

Workers involved in the production of ethanol by the strong-acid process frequently were exposed to diethyl sulfate, which is formed as a by-product of the reaction between ethylene and sulfuric acid (Lynch *et al.* 1979). Analysis of the history of an ethanol plant and interviews with present and former supervisors indicated that exposure to diethyl sulfate vapor was likely from leaky pump seals and when process equipment was opened for manual cleaning, which had to be done frequently. The strong-acid-process workers were also exposed to sulfuric acid mist, coke, tar, heat-transfer-fluid vapor, sulfur trioxide, and ethyl ether. Based on the presence of approximately 30% diethyl sulfate in acid extracts, the maximum vapor concentration over a spill was calculated as 2,000 ppm; however, the actual exposures to workers most likely were much less, because of dilution due to ventilation or air movement. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,260 workers, including 165 women, potentially were exposed to diethyl sulfate in the Textile, Lumber, and Wood Products industries (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of diethyl sulfate on ships.

Department of Transportation (DOT)

Diethyl sulfate is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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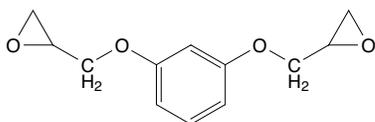
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Diglycidyl Resorcinol Ether

CAS No. 101-90-6

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

Diglycidyl resorcinol ether is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to diglycidyl resorcinol ether caused tumors in two rodent species. Diglycidyl resorcinol ether administered by stomach tube caused forestomach tumors (squamous-cell carcinoma and papilloma) in rats and mice of both sexes (IARC 1985, NTP 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to diglycidyl resorcinol ether.

Properties

Diglycidyl resorcinol ether is an epoxy resin that exists at room temperature as a straw-yellow viscous liquid with a slight phenolic odor. It is slightly soluble in water and miscible with acetone, chloroform, methanol, benzene, and most organic resins. Diglycidyl resorcinol ether has the potential to form explosive peroxides (IARC 1985, Akron 2009, HSDB 2009). Physical and chemical properties of diglycidyl resorcinol ether are listed in the following table.

Property	Information
Molecular weight	222.2 ^a
Specific gravity	1.21 at 25°C/4°C ^a
Melting point	32°C to 33°C ^a
Boiling point	172°C at 0.8 mm Hg ^a
Log K_{ow}	1.23 ^b
Vapor pressure	4×10^{-5} mm Hg at 25°C ^c
Vapor density relative to air	7.7 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Diglycidyl resorcinol ether is used as a liquid epoxy resin and as a reactive diluent in the production of other epoxy resins used in electrical, tooling, adhesive, casting, and laminating applications (IARC 1976). The cured resins made from diglycidyl resorcinol ether are used for coating metal and certain pavements to increase their tensile strength. Diglycidyl resorcinol ether is also used as a curing agent in the production of polysulfide rubber. In recent years, it has been used primarily in the aerospace industry (IARC 1999).

Production

Production of diglycidyl resorcinol ether started in the United States in 1974, and production by its sole U.S. manufacturer was estimated at 4,500 to 45,400 lb in 1977 (IARC 1985). In 2009, diglycidyl resorcinol ether was produced by two manufacturing plants worldwide (one in East Asia and one in China) (SRI 2009) and was available from five suppliers, including three U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of diglycidyl resorcinol ether were found. Reports filed in 1986, 1990, 1994, 1998, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of diglycidyl resorcinol ether totaled 10,000 to 500,000 lb (EPA 2004).

Exposure

The primary route of potential human exposure to diglycidyl resorcinol ether is dermal contact, but exposure by inhalation may also occur (HSDB 2009, TRI 2009). According to EPA's Toxics Release Inventory, 510 lb of diglycidyl resorcinol ether was released to air in 1996. Since then, annual releases to air have remained at 20 lb or less, totaling 1 or 2 lb in 2002 through 2007. In 2001, about 1,100 lb was sent off site for treatment or disposal (TRI 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,856 workers, including 222 women, in the Petroleum and Coal Products, Electric and Electronic Equipment, Transportation Equipment, and Instruments and Related Products industries potentially were exposed to diglycidyl resorcinol ether (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act Toxics Release Inventory: Listed substance subject to reporting requirements.

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3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine

Introduction

3,3'-Dimethoxybenzidine was first listed in the *Third Annual Report on Carcinogens* (1983), and 3,3'-dimethoxybenzidine-based dyes that are metabolized to 3,3'-dimethoxybenzidine (3,3'-dimethoxybenzidine dye class) were first listed in the *Tenth Report on Carcinogens* (2002). The profiles for 3,3'-dimethoxybenzidine and dyes metabolized to 3,3'-dimethoxybenzidine, which are listed (separately) as *reasonably anticipated to be human carcinogens*, follow this introduction.

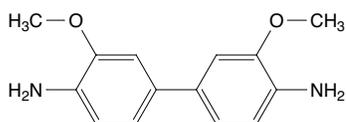
3,3'-Dimethoxybenzidine

CAS No. 119-90-4

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as *o*-dianisidine



Carcinogenicity

3,3'-Dimethoxybenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 3,3'-dimethoxybenzidine caused tumors in two rodent species and at several different tissue sites. Administration of 3,3'-dimethoxybenzidine by stomach tube caused cancer (carcinoma) of the Zymbal gland, skin, and intestine and benign urinary-bladder tumors (papilloma) in rats of both sexes, and dietary exposure to 3,3'-dimethoxybenzidine caused benign forestomach tumors (papilloma) in hamsters (IARC 1974, 1982).

Since 3,3'-dimethoxybenzidine was listed in the *Third Annual Report on Carcinogens*, an additional study in rats has been identified. Administration of the dihydrochloride salt of 3,3'-dimethoxybenzidine in the drinking water increased the combined incidence of benign and malignant tumors of the Zymbal gland (adenoma and carcinoma), liver (hepatocellular adenoma and carcinoma), large intestine (adenomatous polyps and adenocarcinoma), skin (basal-cell or sebaceous-gland adenoma and carcinoma), and oral cavity (squamous-cell papilloma and carcinoma) in both sexes. In males, it also caused cancer of the preputial gland (carcinoma), small intestine (adenocarcinoma), and mesothelium of the testes (metastatic mesothelioma), and in females, it also caused cancer of the clitoral gland (carcinoma) and mammary gland (adenocarcinoma) and increased

the combined incidence of benign and malignant tumors of the uterus and cervix (adenoma and carcinoma) (NTP 1990).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 3,3'-dimethoxybenzidine. No epidemiological studies have been identified on cancer in workers exposed only to 3,3'-dimethoxybenzidine. Most of the workers exposed to 3,3'-dimethoxybenzidine were also exposed to benzidine or other related amines, which are strongly associated with urinary-bladder cancer in humans (IARC 1974, 1982, 1987).

Properties

3,3'-Dimethoxybenzidine is an aromatic amine that is initially a colorless crystal but turns violet upon standing at room temperature (HSDB 2009). It is practically insoluble in water, but is soluble in alcohol, benzene, ether, chloroform, acetone, and probably most other organic solvents. It is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 3,3'-dimethoxybenzidine are listed in the following table.

Property	Information
Molecular weight	244.3 ^a
Melting point	137°C ^a
Boiling point	356°C ^b
Log <i>K</i> _{ow}	1.81 ^a
Water solubility	0.060 g/L at 25°C ^a
Vapor pressure	1.25 × 10 ⁻⁷ mm Hg at 25°C ^b
Vapor density relative to air	8.43 ^a
Dissociation constant (p <i>K</i> _a)	4.2 at 25°C ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cSRC 2010.

Use

3,3'-Dimethoxybenzidine is used almost exclusively as a chemical intermediate for producing dyes and pigments. In 1971, the Society of Dyers and Colourists reported its use in the production of 89 dyes (see Dyes Metabolized to 3,3'-Dimethoxybenzidine, below). 3,3'-Dimethoxybenzidine is also used as a chemical intermediate to produce *o*-dianisidine diisocyanate for use in adhesives and as a component of polyurethanes. Other uses are as a dye for paper, plastics, rubber, and textiles and as a test substance for detection of metals, thiocyanates, and nitrites (IARC 1974, HSDB 2009).

Production

3,3'-Dimethoxybenzidine has been produced commercially since the 1920s. Data on U.S. production of 3,3'-dimethoxybenzidine were last reported in 1967, when five U.S. companies produced about 367,000 lb. In 1971, only two U.S. companies were known to produce 3,3'-dimethoxybenzidine, and U.S. imports of 3,3'-dimethoxybenzidine were about 273,000 lb (IARC 1974). In 2009, no U.S. manufacturers of 3,3'-dimethoxybenzidine were identified (SRI 2009), but 3,3'-dimethoxybenzidine was available from 25 U.S. suppliers, and 3,3'-dimethoxybenzidine dihydrochloride from 13 U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to 3,3'-dimethoxybenzidine are inhalation and dermal contact (HSDB 2009). The general population could be exposed to 3,3'-dimethoxybenzidine as a trace contaminant in products made with 3,3'-dimethoxybenzidine (e.g., azo dyes, pigments, adhesives, resins, and polyurethane elastomers). No data were found on the quantities of 3,3'-dimethoxyben-

zidine in consumer products. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, only small amounts of 3,3'-dimethoxybenzidine and 3,3'-dimethoxybenzidine dihydrochloride were released to the environment between 1988 and 2008. In 2008, one facility released 255 lb of 3,3'-dimethoxybenzidine dihydrochloride (TRI 2010).

Exposure to 3,3'-dimethoxybenzidine can occur during its use as a chemical intermediate in the production of azo dyes and *o*-dianisidine diisocyanate formulations, in textile processing, and in packaging processes. Workers potentially exposed include dye makers and *o*-dianisidine diisocyanate production workers (HSDB 2009). However, present dye production processes for 3,3'-dimethoxybenzidine and its dye derivatives generally are closed systems that minimize worker exposure. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,481 workers potentially were exposed to 3,3'-dimethoxybenzidine (NIOSH 1990). Another study (cited by the National Toxicology Program in 1986) estimated that about 1,000 workers were exposed to 3,3'-dimethoxybenzidine during dye manufacturing, but that as many as 15,000 workers potentially were exposed in the various dye-application industries (HSDB 2009).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics release inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 3,3'-dimethoxybenzidine = U091.

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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SRC. 2010. *Interactive PhysProp Database Demo*. Syracuse Research Corporation. <http://www.syrres.com/what-we-do/databaseforms.aspx?id=386> and search on CAS number. Last accessed: 1/19/10.

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Dyes Metabolized to 3,3'-Dimethoxybenzidine (3,3'-Dimethoxybenzidine Dye Class)

CAS No.: none assigned

Reasonably anticipated to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

3,3'-Dimethoxybenzidine-based dyes that are metabolized to 3,3'-dimethoxybenzidine are *reasonably anticipated to be human carcinogens* based on studies on mechanisms of carcinogenesis and cancer studies in experimental animals, which have provided the following evidence:

- Dyes in this class released free 3,3'-dimethoxybenzidine in studies on metabolism in experimental animals (Lynn *et al.* 1980, Bowman *et al.* 1983).
- 3,3'-Dimethoxybenzidine is carcinogenic in experimental animals (see 3,3'-Dimethoxybenzidine, above).
- A representative 3,3'-dimethoxybenzidine-based dye, C.I. direct blue 15, is carcinogenic in experimental animals.
- The profile of tumors caused by 3,3'-dimethoxybenzidine and direct blue 15 is similar to that caused by structurally related chemicals.

Studies on Mechanisms of Carcinogenesis

3,3'-Dimethoxybenzidine is structurally similar to both benzidine, which is listed in the Report on Carcinogens as *known to be a human carcinogen*, and 3,3'-dimethylbenzidine, which is listed as *reasonably anticipated to be a human carcinogen*. The pattern of tumors observed for direct blue 15 (NTP 1992) and 3,3'-dimethoxybenzidine (NTP 1990) in rats is similar to that observed for the structurally similar chemical 3,3'-dimethylbenzidine (NTP 1991a) and the 3,3'-dimethylbenzidine-based dye C.I. acid red 114 (NTP 1991b). In rats, these four chemicals caused tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland, and clitoral gland, as well as at other tissue sites.

Like benzidine and 3,3'-dimethylbenzidine, 3,3'-dimethoxybenzidine is used to synthesize many dyes, through azo linking of various chromophores to the base chemical. The azo bonds of 3,3'-dimethoxybenzidine-based dyes are chemically similar regardless of the chromophore used, and they are easily broken by azo-reductase enzymes to form free 3,3'-dimethoxybenzidine and free chromophore(s), a process that was observed in rats and dogs (Lynn *et al.* 1980, Bowman *et al.* 1983). Quantitative evidence demonstrated that both of the 3,3'-dimethoxybenzidine-based dyes studied (direct blue 1 and direct blue 15) were nearly completely metabolized to free 3,3'-dimethoxybenzidine (Lynn *et al.* 1980). Bacteria in the animals' gastrointestinal tract are thought to be the primary agents forming free 3,3'-dimethoxybenzidine, which is absorbed by the intestine, metabolized, and excreted in the urine and feces (Cerniglia *et al.* 1982, Morgan *et al.*

1994). Species differences in metabolism of 3,3'-dimethoxybenzidine in the liver or target tissues probably account for species differences in tissue sites of tumors (Morgan *et al.* 1994). 3,3'-Dimethoxybenzidine-based dyes are mutagenic in bacteria when tested with mammalian metabolic activation and an azo-reductive preincubation protocol (NTP 1991a). It is assumed that the reductive breakdown process forms 3,3'-dimethoxybenzidine, which is known to cause mutations in bacteria (Haworth *et al.* 1983). 3,3'-Dimethoxybenzidine has been found in urine from workers exposed to 3,3'-dimethoxybenzidine-based dyes; however, contamination of the dye with 3,3'-dimethoxybenzidine could not be ruled out (Lowry *et al.* 1980, NIOSH 1980).

There is no evidence to suggest that mechanisms by which these substances cause tumors in experimental animals would not also operate in humans.

Cancer Studies in Experimental Animals

A representative 3,3'-dimethoxybenzidine-based dye, direct blue 15, is carcinogenic in rats (NTP 1992). Exposure to direct blue 15 in the drinking water caused benign and/or malignant tumors of the skin, Zymbal gland, liver, oral cavity, and small and large intestines in both sexes, the preputial gland in males, and the clitoral gland and uterus in females. It also caused mononuclear-cell leukemia in females, and increased incidences of mononuclear-cell leukemia and brain tumors observed in males may also have been related to exposure to direct blue 15.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3,3'-dimethoxybenzidine-based dyes.

Properties

All dimethoxybenzidine-based dyes have the characteristic diazotized dimethoxybenzidine nucleus, but differ with respect to the chemical groups attached at the diazo linkages. Most of the dyes in this class contain two or three azo groups, but they can contain more. They all exist at room temperature as colored powders (in a wide range of hues) and have negligible vapor pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. There are no rigid chemical specifications for dyes, including dimethoxybenzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer (IARC 1982). Also, because various dyes are mixed together to produce particular colors, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

The Society of Dyers and Colourists reported the production of 89 3,3'-dimethoxybenzidine-based dyes in 1971, including pigment orange 16, direct blue 1, direct blue 15, direct blue 8, direct blue 76, direct blue 98, and direct blue 218. 3,3'-Dimethoxybenzidine-based dyes are used to color paper, plastics, rubber, and textiles, and in the past were used to dye leather (IARC 1974, HSDB 2009).

Production

In 2009, no information on production of dyes previously identified as derived from 3,3'-dimethoxybenzidine was found; however, the dyes were available from numerous suppliers worldwide, including at least six U.S. suppliers (ChemSources 2010). All synthetic organic dyes and dye intermediates are included in a single category for reporting of U.S. imports and exports; no data were available on imports or exports of specific dye products.

Exposure

Most environmental exposure to 3,3'-dimethoxybenzidine and 3,3'-dimethoxybenzidine-based dyes is through contact with contaminated air, water, or soil (HSDB 2009). The general population may also be exposed via contact with paper or fabric products containing these dyes or through consumer use of the dyes.

Occupational exposure to 3,3'-dimethoxybenzidine-based dyes may occur by inhalation of dust or mists, accidental ingestion, or dermal contact. Most occupational exposure is to workers in dye-manufacturing and -processing plants. In 1986–87, the U.S. Environmental Protection Agency, the American Textile Manufacturers Institute, and the Toxicological Association of the Dyestuffs Manufacturing Industry conducted a joint survey to estimate airborne concentrations of dye dust in dye-weighing rooms of facilities where powdered dyes were used to dye and print textiles. The estimated mean airborne concentration of total dye in 24 randomly monitored plants was 0.085 mg/m³ (EPA 1990). However, current production processes using 3,3'-dimethoxybenzidine and 3,3'-dimethoxybenzidine-based dyes generally are closed systems that minimize worker exposure (HSDB 2009). Occupational exposure may also occur in clinical laboratories where 3,3'-dimethoxybenzidine is used in chemical tests. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,481 workers potentially were exposed to 3,3'-dimethoxybenzidine (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Direct blue 218 is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

3,3'-Dimethoxybenzidine-based dyes are listed as potential occupational carcinogens.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

3,3'-Dimethoxybenzidine-based dyes are listed as potential occupational carcinogens.

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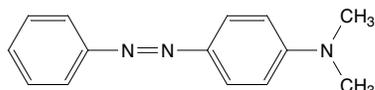
4-Dimethylaminoazobenzene

CAS No. 60-11-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *para*-dimethylaminoazobenzene, *N,N*-dimethyl-4-aminoazobenzene, or butter yellow



Carcinogenicity

4-Dimethylaminoazobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4-Dimethylaminoazobenzene caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. In rats of unspecified sex, oral administration or subcutaneous injection of 4-dimethylaminoazobenzene caused liver cancer (hepatocellular carcinoma) that metastasized to other organs. Liver tumors also were observed in rats of unspecified sex administered 4-dimethylaminoazobenzene by intraperitoneal injection. Following subcutaneous injection of 4-dimethylaminoazobenzene in newborn mice, males developed liver tumors by 1 year of age. In dogs of unspecified sex, oral exposure to 4-dimethylaminoazobenzene caused benign urinary-bladder tumors (papilloma). Dermal exposure to 4-dimethylaminoazobenzene caused skin cancer (squamous- or basal-cell carcinoma or anaplastic carcinoma) in male rats, but not in mice. (IARC 1975).

Since 4-dimethylaminoazobenzene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Dietary administration of 4-dimethylaminoazobenzene to male mice for 14 months resulted in development of benign and

malignant liver tumors (adenoma after 104 days and carcinoma after 10 months) (Caballero *et al.* 2004). Following intraperitoneal injection with 4-dimethylaminoazobenzene before the age of 22 days, male rats developed liver cancer (hepatocellular carcinoma) by the age of 2 years. Intraperitoneal injection of 12-day-old mice with 4-dimethylaminoazobenzene increased the incidence of liver tumors and number of tumors per animal in males (Delclos *et al.* 1984). Implantation of pellets containing 4-dimethylaminoazobenzene in the livers of male rats increased the incidence of liver cancer (hepatocellular carcinoma); however, implantation in the kidney did not cause kidney tumors (Aterman 1987).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4-dimethylaminoazobenzene.

Properties

4-Dimethylaminoazobenzene is an azo amine dye that exists at room temperature as yellow crystalline leaflets. It is practically insoluble in water, but is soluble in alcohol, benzene, chloroform, ether, petroleum ether, mineral acids, and oils, and is very soluble in pyridine. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4-dimethylaminoazobenzene are listed in the following table.

Property	Information
Molecular weight	225.3 ^a
Density	1.2 g/cm ^{3b}
Melting point	114°C to 117°C ^a
Boiling point	371°C ^b
Log <i>K</i> _{ow}	4.58 ^a
Water solubility	0.23 mg/L at 25°C ^c
Vapor pressure	3.3 × 10 ⁻⁷ mm Hg ^a
Vapor density relative to air	7.78 ^a
Dissociation constant (p <i>K</i> _a)	2.96 at 25°C ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

4-Dimethylaminoazobenzene is an industrial chemical that has been used to color polishes and other wax products, polystyrene, gasoline, and soap. It has been used as a pH indicator, especially for gastric juices, and as a spot test for identification of peroxidized fats. It is also used as a positive-control substance to induce liver cancer in experimental animals. Previously, it was used as a colorant (butter yellow) in hair creams (brilliantine) in Scandinavia (IARC 1975, Akron 2009, HSDB 2009). 4-Dimethylaminoazobenzene was approved for use as a food additive in 1918, but was withdrawn six months later because of contact dermatitis from occupational exposure (IARC 1975).

Production

4-Dimethylaminoazobenzene was first made in 1876, and large-scale production in the United States was first reported in 1914 (IARC 1975). In 1972, 4-dimethylaminoazobenzene was one of a group of at least 20 colorants with U.S. production totaling 466,000 kg (1 million pounds); however, no individual production data were available. In 2009, no producers of 4-dimethylaminoazobenzene were identified worldwide (SRI 2009), but it was available from 24 suppliers, including 13 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports were found specifically for 4-dimethylaminoazobenzene.

Exposure

The routes of potential human exposure to 4-dimethylaminoazobenzene are inhalation, dermal contact, and ingestion. 4-Dimethylaminoazobenzene was a component of brilliantine, which was commonly applied after men's haircuts in some portions of Europe until about 1950 (Skov and Lynge 1994).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, no environmental releases of 4-dimethylaminoazobenzene occurred in 2000. Releases totaled 750 lb in 2001 and 250 lb in 2002, and have since remained at about the same level. In 2009, one facility released 256 lb of 4-dimethylaminoazobenzene to an off-site hazardous waste landfill (TRI 2009). When released to air, 4-dimethylaminoazobenzene is expected primarily to bind to particulate matter; however, the vapor-phase fraction may be subject to direct photolysis or reaction with photochemically produced hydroxyl radicals, with a half-life of 7 hours. When released to surface water, 4-dimethylaminoazobenzene is expected to bind to sediment or to bioaccumulate in aquatic organisms; it will not hydrolyze and may be subject to biodegradation. When released to soil, it will most likely bind to soil particles and not leach into groundwater; however, its mobility is affected by soil pH (HSDB 2009).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,453 workers in the Health Services industry, including 996 women, and an additional 23 workers in the Textile Mill Products industry potentially were exposed to 4-dimethylaminoazobenzene (NIOSH 1990). Also potentially exposed to 4-dimethylaminoazobenzene are laboratory workers who use it as a positive-control substance in studies of liver cancer or as a reagent in determining free hydrochloric acid in gastric juices (IARC 1975, HSDB 2009).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 4-dimethylaminoazobenzene = U093.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine

Introduction

3,3'-Dimethylbenzidine was first listed in the *Third Annual Report on Carcinogens* (1983) and was re-reviewed for the *Tenth Report on Carcinogens* (2002). 3,3'-Dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine (3,3'-dimethylbenzidine dyes class) were first listed in the *Tenth Report on Carcinogens* (2002). The profiles for 3,3'-dimethylbenzidine and dyes metabolized to 3,3'-dimethylbenzidine, which are listed (separately) as *reasonably anticipated to be human carcinogens*, follow this introduction.

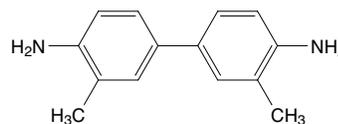
3,3'-Dimethylbenzidine

CAS No. 119-93-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as *o*-tolidine



Carcinogenicity

3,3'-Dimethylbenzidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

3,3'-Dimethylbenzidine caused tumors in rats at numerous tissue sites and by two different routes of exposure. Administration of the dihydrochloride salt of 3,3'-dimethylbenzidine in the drinking water caused benign and/or malignant tumors of the Zymbal gland (adenoma or carcinoma), liver (hepatocellular adenoma or carcinoma), skin (basal-cell adenoma or squamous-cell papilloma or carcinoma), preputial and clitoral glands (adenoma or carcinoma), and large intestine (adenomatous polyps) in rats of both sexes. In males, it also caused cancer of the small intestine (adenocarcinoma) and benign lung tumors (adenoma), and in females, it also caused mammary-

gland cancer (adenocarcinoma) and benign or malignant oral-cavity tumors (squamous-cell papilloma or carcinoma) (NTP 1991). Exposure of rats (of unspecified sex) to commercial-grade or purified 3,3'-dimethylbenzidine by subcutaneous injection primarily caused Zymbal-gland cancer (carcinoma) (IARC 1972).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3,3'-dimethylbenzidine. However, one study found that occupational exposure to a mixture of arylamine amine products, including 3,3'-dimethylbenzidine, was associated with an increased incidence of urinary-bladder cancer (Ouellet-Hellstrom and Rench 1996).

Properties

3,3'-Dimethylbenzidine is an aromatic amine that exists at room temperature as a white-to-reddish powder or crystals. It is slightly soluble in water and soluble in ethanol, ether, and dilute acids. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of 3,3'-dimethylbenzidine are listed in the following table

Property	Information
Molecular weight	212.3 ^a
Specific gravity	1.234 g/mL ^b
Melting point	129°C to 131°C ^a
Boiling point	300°C ^a
Log K_{ow}	2.34 ^a
Water solubility	1.3 g/L at 25°C ^a
Vapor pressure	6.9×10^{-7} mm Hg at 25°C ^a
Dissociation constant (pK_a)	4.5 at 25°C ^a

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

Dimethylbenzidine is used as a dye or as an intermediate for producing dyestuffs and pigments; it is used to color textiles, leather, plastic, rubber, and paper (see Dyes Metabolized to 3,3'-Dimethylbenzidine, below). 3,3'-Dimethylbenzidine is also used as a laboratory reagent for the detection of blood, gold, and chlorine and as a curing agent for urethane resins (IARC 1972, NTP 1991, HSDB 2009).

Production

In 2009, 3,3'-dimethylbenzidine was produced by seven manufacturers worldwide, including one in the United States, one each in Europe and East Asia, and two each in China and India (SRI 2009), and was available from 34 suppliers, including 20 U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to 3,3'-dimethylbenzidine are inhalation, dermal contact, and ingestion (IARC 1972, HSDB 2009). The general population may be exposed through contact with dyes or pigments in final consumer products that may contain small residual amounts of 3,3'-dimethylbenzidine (NTP 1991). Indirect exposure may occur through dimethylbenzidine-based dyes that can be metabolized to 3,3'-dimethylbenzidine by the liver or bacteria in the gastrointestinal tract (NTP 1991) or on the skin. Although dimethylbenzidine-based dyes may not be absorbed dermally to any substantial degree, 3,3'-dimethylbenzidine itself is known to easily penetrate the skin, and it was demonstrated that an azo dye (C.I. direct blue 14) could be metabolized by numerous strains of common skin bacteria to yield 3,3'-dimethylbenzidine (Platzek *et al.* 1999).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, no more than 270 lb of 3,3'-dimethylbenzidine has been released to the environment in any year since 1989, and no more than 17 lb has been released to air. In 2007, one facility released 10 lb of 3,3'-dimethylbenzidine (TRI 2009). If released to air, 3,3'-dimethylbenzidine will exist as both a vapor and particulate. The vapor fraction will be degraded by photochemically produced hydroxyl radicals, with a half-life of 3 hours, and it may be sensitive to direct photolysis. If released to water, 3,3'-dimethylbenzidine is expected to adsorb to suspended solids and sediment, and not to volatilize or undergo hydrolysis. If released to soil, it is expected to bind to humic materials with moderate mobility at neutral pH; however, mobility may decrease under acidic conditions. Limited data suggest that 3,3'-dimethylbenzidine may slowly biodegrade in the environment (HSDB 2009).

Workers potentially exposed to 3,3'-dimethylbenzidine include dye makers, repackagers of 3,3'-dimethylbenzidine and dimethylbenzidine-based dyes, and analytical chemistry laboratory workers (NIOSH 1978). It has been recommended that analytical methods for determining chlorine in water using 3,3'-dimethylbenzidine be replaced with the methyl-orange method, which uses less hazardous reagents (IPCS 1982). 3,3'-Dimethylbenzidine was found in the urine of dye-manufacturing workers who had been indirectly exposed through contact with 3,3'-dimethylbenzidine-based dyes (NTP 1991). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,640 workers including 6,005 women (mostly in the health-services sector), potentially were exposed to 3,3'-dimethylbenzidine (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 3,3'-dimethylbenzidine = U095.

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 0.02 mg/m³ (60-min exposure).

Listed as a potential occupational carcinogen.

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Dyes Metabolized to 3,3'-Dimethylbenzidine (3,3'-Dimethylbenzidine Dye Class)

CAS No.: none assigned

Reasonably anticipated to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

3,3'-Dimethylbenzidine-based dyes that are metabolized to 3,3'-dimethylbenzidine are *reasonably anticipated to be human carcinogens* based cancer studies in experimental animals and studies on mechanisms of carcinogenesis, which have provided the following evidence:

- 3,3'-Dimethylbenzidine is carcinogenic in rats of both sexes.
- Metabolism of 3,3'-dimethylbenzidine-based dyes to release free 3,3'-dimethylbenzidine is a generalized phenomenon that occurs in all animal species studied (Lynn *et al.* 1980, Bowman *et al.* 1982).
- A representative 3,3'-dimethylbenzidine-based dye, C.I. acid red 114, is carcinogenic in experimental animals.
- The profile of tumors caused by 3,3'-dimethylbenzidine and acid red 114 is similar to that caused by structurally related chemicals.

Cancer Studies in Experimental Animals

Oral exposure to a representative 3,3'-dimethylbenzidine-based dye, acid red 114, caused tumors in rats at numerous tissue sites (NTP 1991a). Acid red 114 administered in the drinking water caused benign and/or malignant tumors of the liver, skin, and Zymbal gland in rats of both sexes and of the clitoral gland, oral-cavity epithelium, small and large intestines, and lung in female rats. Increased incidences of tumors of the oral-cavity epithelium, adrenal gland, and lung in male rats and of mononuclear-cell leukemia and cancer of the mammary gland (adenocarcinoma) and adrenal gland (pheochromocytoma) in female rats also may have been related to exposure to acid red 114.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 3,3'-dimethylbenzidine-based dyes.

Studies on Mechanisms of Carcinogenesis

3,3'-Dimethylbenzidine is structurally similar to benzidine, which is listed in the Report on Carcinogens as *known to be a human carcino-*

gen, and 3,3'-dimethoxybenzidine, which is listed as *reasonably anticipated to be a human carcinogen*. The pattern of tumors observed for acid red 114 (NTP 1991a) and 3,3'-dimethylbenzidine (NTP 1991b) in rats is similar to that observed for the structurally similar chemical 3,3'-dimethoxybenzidine (NTP 1990) and the 3,3'-dimethoxybenzidine-based dye C.I. direct blue 15 (NTP 1992). In rats, these four chemicals caused tumors of the skin, Zymbal gland, liver, oral cavity, gastrointestinal tract, preputial gland, and clitoral gland, as well as at other tissue sites.

Like benzidine and 3,3'-dimethoxybenzidine, 3,3'-dimethylbenzidine is used to synthesize many dyes through azo linking of various chromophores to the base chemical. The azo bonds of 3,3'-dimethylbenzidine-based dyes are chemically similar regardless of the chromophore used, and they are easily broken via reduction by chemicals or enzymes to form free 3,3'-dimethylbenzidine and free chromophore(s). A number of bacteria catalyze this process, including *Escherichia coli*, which is found in the human gastrointestinal tract (Cerniglia *et al.* 1982, Morgan *et al.* 1994). This reductive process has also been found in rats, hamsters, and dogs (Lynn *et al.* 1980, Bowman *et al.* 1983, Nony *et al.* 1983). Bacteria in the animals' gastrointestinal tract are thought to be the primary agents of this metabolism (Cerniglia *et al.* 1982, Morgan *et al.* 1994). 3,3'-Dimethylbenzidine-based dyes are mutagenic in bacteria when tested with mammalian metabolic activation and an azo-reductive preincubation protocol (NTP 1991a). It is assumed that the breakdown process results in the formation of 3,3'-dimethylbenzidine, which is known to cause mutations in bacteria (Haworth *et al.* 1983).

There is no evidence to suggest that mechanisms by which these substances cause tumors in experimental animals would not also operate in humans.

Properties

All dimethylbenzidine-based dyes have the characteristic diazotized dimethylbenzidine nucleus, but they differ with respect to the chemical groups attached at the diazo linkages. They all exist as colored powders (in a wide range of hues) at room temperature and have negligible vapor pressures. Their water solubility varies, but it is sufficient for dyeing in aqueous solution. There are no rigid chemical specifications for dyes, including dimethylbenzidine-based dyes; therefore, their composition varies according to the shade and intensity requirements of the customer. Also, because various dyes are mixed together to produce particular colors, the final products are more accurately described as mixtures of substances than as specific chemical compounds (NIOSH 1980).

Use

3,3'-Dimethylbenzidine-based dyes and pigments are used in printing textiles, as biological stains, and in color photography (HSDB 2009). In 1972, the Colour Index listed nearly 100 dyes derived from 3,3'-dimethylbenzidine (IARC 1972).

Production

In 2009, no information on production of dyes previously identified as derived from 3,3'-dimethylbenzidine was found; however, the dyes were available from numerous suppliers worldwide, including at least ten U.S. suppliers (ChemSources 2009). All synthetic organic dyes and dye intermediates are included in a single category for reporting of U.S. imports and exports; no data were available on imports or exports of specific dye products.

Exposure

The general population may be exposed via contact with textiles and papers containing 3,3'-dimethylbenzidine-based dyes (NTP 1991a). Occupational exposure to 3,3'-dimethylbenzidine-based dyes may occur by inhalation of dust or mist, accidental ingestion, or dermal contact. Most occupational exposure is of workers in dye-manufacturing and -processing plants. In 1986–87, the U.S. Environmental Protection Agency, the American Textile Manufacturers Institute, and the Toxicological Association of the Dyestuffs Manufacturing Industry conducted a joint survey to estimate airborne concentrations of dye dust in dye-weighing rooms of facilities where powdered dyes were used to dye and print textiles. The estimated mean airborne concentration of total dye in 24 randomly monitored plants was 0.085 mg/m³ (EPA 1990). Workers in other occupations may be exposed to small quantities of 3,3'-dimethylbenzidine-based dyes, including water and sewage plant attendants, chemical test tape or kit makers, and swimming-pool service representatives (NIOSH 1978)

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: C.I. acid red 114 is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

3,3'-Dimethylbenzidine-based dyes are listed as potential occupational carcinogens.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

3,3'-Dimethylbenzidine-based dyes are listed as potential occupational carcinogens.

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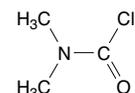
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Dimethylcarbamoyl Chloride

CAS No. 79-44-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Dimethylcarbamoyl chloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dimethylcarbamoyl chloride caused tumors in mice at two different tissue sites and by several different routes of administration. In female mice, dermal exposure to dimethylcarbamoyl chloride caused benign and malignant skin tumors (papilloma and carcinoma), and exposure by subcutaneous or intraperitoneal injection caused tumors at the injection site (sarcoma) (IARC 1976). Since dimethylcarbamoyl chloride was listed in the *Second Annual Report on Carcinogens*, an additional study in rodents has been identified. Dimethylcarbamoyl chloride administered by inhalation caused cancer of the nasal tract (carcinoma) of rats and hamsters (IARC 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dimethylcarbamoyl chloride. The only available study had very small numbers of exposed workers (IARC 1976).

Properties

Dimethylcarbamoyl chloride is an alkyl carbamoyl chloride that exists at room temperature as a clear, colorless liquid. It hydrolyzes rapidly in water (IARC 1976). Physical and chemical properties of dimethylcarbamoyl chloride are listed in the following table.

Property	Information
Molecular weight	107.5 ^a
Density	1.17 g/mL at 25°C ^a
Melting point	-33°C ^a
Boiling point	167°C ^a
Log K _{ow}	-0.72 ^b
Water solubility	459 g/L at 25°C ^b
Vapor pressure	1.95 mm Hg at 25°C ^a
Vapor density relative to air	3.73 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Dimethylcarbamoyl chloride has been used primarily as a chemical intermediate in the production of dyes, pharmaceuticals, pesticides, and rocket fuel (IARC 1999, HSDB 2009).

Production

Dimethylcarbamoyl chloride has been produced since 1961 (IARC 1999). In 2009, it was produced commercially by one manufacturer in Europe and two manufacturers in India (SRI 2009) and was available from 17 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of dimethylcarbamoyl chloride were found. Under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule, production plus imports of dimethylcarbamoyl chloride totaled between 10,000 and 500,000 lb in 1990; no other inventory update reports were filed (EPA 2004).

Exposure

Potential routes of human exposure to dimethylcarbamoyl chloride are inhalation, ingestion, and dermal contact. Dimethylcarbamoyl chloride has been released to the environment as a result of its manufacture and use as an intermediate in the manufacture of pesticides and drugs (HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of dimethylcarbamoyl chloride have remained between 98 and 366 lb since 1997, with most releases to air and the remainder to off-site non-hazardous-waste landfills. In 2007, one facility released 260 lb of dimethylcarbamoyl chloride; most (255 lb) was released to an off-site hazardous-waste landfill, and the remainder to air (TRI 2009). Dimethylcarbamoyl chloride is not expected to persist in the environment, because it hydrolyzes rapidly in water and moist soil (HSDB 2009). Significant potential human exposure to dimethylcarbamoyl chloride is restricted to chemical workers, pesticide formulators, dye makers, and pharmaceutical workers.

Regulations

Department of Transportation (DOT)

Dimethylcarbamoyl chloride is considered a hazardous material, and special requirements have been set for marking, labeling, and transportation of this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of dimethylcarbamoyl chloride = U097.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.005 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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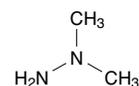
1,1-Dimethylhydrazine

CAS No. 57-14-7

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as unsymmetrical dimethylhydrazine or UDMH



Carcinogenicity

1,1-Dimethylhydrazine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure of mice to 1,1-dimethylhydrazine caused tumors at several different tissue sites. Following administration of 1,1-dimethylhydrazine in drinking water, high incidences of blood-vessel cancer (angiosarcoma) in various organs were observed in mice of both sexes; tumors of the kidneys, lungs, and liver also were observed. Administration of 1,1-dimethylhydrazine by stomach tube increased the incidence of lung tumors and the number of tumors per animal in female mice (IARC 1974).

Since 1,1-dimethylhydrazine was listed in the *Fourth Annual Report on Carcinogens*, additional studies in experimental animals have been identified. 1,1-Dimethylhydrazine administered by subcutaneous injection increased the incidence of benign and malignant peripheral nerve sheath tumors (neurofibrosarcoma and melanotic and unpigmented schwannoma) in hamsters of both sexes (IARC 1999).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1,1-dimethylhydrazine.

Properties

1,1-Dimethylhydrazine exists at room temperature as a clear, colorless liquid with a fishy odor. It is miscible with water, ether, hydrocarbons, and dimethylformamide and is very soluble in methanol and ethanol (HSDB 2009). It is stable under normal temperatures and pressures, but is considered very flammable and can be ignited eas-

ily (Akron 2009). Physical and chemical properties of 1,1-dimethylhydrazine are listed in the following table.

Property	Information
Molecular weight	60.1
Specific gravity	0.78 at 25°C/25°C
Melting point	-58°C
Boiling point	64°C at 760 mm Hg
Log K_{ow}	-1.19
Water solubility	1,000 g/L
Vapor pressure	167 mm Hg at 25°C
Vapor density relative to air	1.94
Dissociation constant (pK_a)	7.21 at 25°C

Source: HSDB 2009.

Use

1,1-Dimethylhydrazine is used primarily as a component of jet and rocket fuels. Other uses include as an intermediate for chemical synthesis, as a stabilizer for organic peroxide fuel additives, as an absorbent for acid gases, as a plant growth control agent, and in photography (ATSDR 1997, IARC 1999, HSDB 2009).

Production

Production of 1,1-dimethylhydrazine was first reported to the U.S. Tariff Commission in 1956 (IARC 1974). Production was 45 metric tons (99,000 lb) in 1977 and 4.5 metric tons (9,900 lb) in 1982 (ATSDR 1997, HSDB 2009). In 2009, 1,1-dimethylhydrazine was produced by four manufacturers worldwide, including one in the United States (SRI 2009), and was available from 17 suppliers, including 9 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,1-dimethylhydrazine totaled 500,000 pounds to 1 million pounds in 1986, 1990, and 1994 and 10,000 to 500,000 lb in 1998 and 2002 (EPA 2004).

Exposure

The primary routes of potential human exposure to 1,1-dimethylhydrazine are inhalation, ingestion, and dermal contact (HSDB 2009). The general population potentially could be exposed by ingestion of residues present on foods treated with 1,1-dimethylhydrazine. In the past, humans have been exposed to 1,1-dimethylhydrazine following ingestion of fruits sprayed with the plant growth regulator Alar (daminozide). 1,1-Dimethylhydrazine was identified as a hydrolysis product of daminozide in processed fruit. Daminozide is no longer registered for use on food plants in the United States (ATSDR 1997). 1,1-Dimethylhydrazine has been detected in tobacco products (at concentrations of up to 147 ng/g); therefore, people who chew tobacco may be exposed to small amounts of 1,1-dimethylhydrazine (Schmeltz *et al.* 1977). However, it has been detected in cigarette mainstream smoke (Diekmann *et al.* 2002). The potential for exposure to 1,1-dimethylhydrazine may be higher for people who live near military installations where the chemical is used as an aerospace propellant or for people who live near hazardous-waste sites contaminated with hydrazines. In the mid 1970s, 1,1-dimethylhydrazine was measured in the air near Rocky Mountain Arsenal at levels of up to 1.7 ppm (4.1 mg/m³) (limit of detection = 0.001 ppm [0.002 mg/m³]) (HSDB 2009). In 1997, 1,1-dimethylhydrazine was identified as a contaminant at three hazardous-waste sites on EPA's National Priorities List.

Environmental exposure to 1,1-dimethylhydrazine is expected to be very low, because it degrades rapidly in the environment (HSDB 2009). Between 1988 and 2007, the largest environmental release of 1,1-dimethylhydrazine reported by EPA's Toxics Release Inventory occurred in 1988, when 13,188 lb was released, predominantly to

on-site landfills or surface impoundments and to air. Since 1988, the largest releases have been 2,320 lb in 1989 and 1,468 lb in 2001. The smallest reported release occurred in 2007, when one U.S. facility released 15 lb of 1,1-dimethylhydrazine, including 5 lb to air and 10 lb to an off-site hazardous-waste landfill (TRI 2009). If released to air, 1,1-dimethylhydrazine will exist entirely in the vapor phase and will react quickly with ozone, with a half-life of about 16.5 minutes, or with hydroxyl radicals, with an estimated half-life of 6 days. 1,1-Dimethylhydrazine has not been detected in environmental samples of water or soil (HSDB 2009).

Workers may potentially be exposed to 1,1-dimethylhydrazine during its production, transportation, use as a chemical intermediate, or application to control the growth of crops and vegetation, especially if proper protective equipment is not used (ATSDR 1997). Greenhouse workers who use daminozide on non-food plants may be exposed to small amounts of 1,1-dimethylhydrazine (ATSDR 1997). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,917 workers (in the Chemicals and Allied Products industry) potentially were exposed to 1,1-dimethylhydrazine (NIOSH 1990).

Regulations

Department of Transportation (DOT)

1,1-Dimethylhydrazine is considered a hazardous material and marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use of 1,1-dimethylhydrazine is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 1,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 1,1-dimethylhydrazine = U098, K107, K108, K109, K110.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.5 ppm (1 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 0.06 ppm (0.15 mg/m³) (2-h exposure).

Immediately dangerous to life and health (IDLH) limit = 15 ppm.

Listed as a potential occupational carcinogen.

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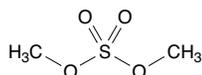
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select 1,1-Dimethyl Hydrazine.

Dimethyl Sulfate

CAS No. 77-78-1

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Dimethyl sulfate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dimethyl sulfate caused tumors in rats at several different tissue sites and by several different routes of exposure. Inhalation exposure to dimethyl sulfate caused cancer of the nasal cavity (squamous-cell carcinoma) and other local tumors. Exposure by subcutaneous injection caused cancer at the injection site (sarcoma). Dimethyl sulfate administered to pregnant rats by intravenous injection caused tumors of the nervous system in the offspring (IARC 1974).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to dimethyl sulfate. At the time dimethyl sulfate was listed in the *Second Annual Report on Carcinogens*, four cases of bronchial cancer (carcinoma) had been reported in men occupationally exposed to dimethyl sulfate. Since that time, two additional cases of cancer in workers exposed to dimethyl sulfate have been identified. In one case, a man who had been exposed to dimethyl sulfate for six years developed primary cancer of the eye (choroidal melanoma). In the second case, a man who had been exposed for seven years to "small amounts" of dimethyl sulfate but also to larger amounts of the known human carcinogens bis(chloromethyl) ether and chloromethyl methyl ether developed lung cancer (pulmonary carcinoma) (IARC 1982).

Properties

Dimethyl sulfate is the dimethyl ester of sulfuric acid, which exists at room temperature as a colorless, oily liquid with a faint onion-like odor. It is soluble in water, ether, dioxane, acetone, benzene, and other aromatic hydrocarbons, miscible with ethanol, and sparingly soluble in carbon disulfide. It is stable under normal temperatures and pressures, but hydrolyzes rapidly in water at or above 18°C (HSDB

2009). Physical and chemical properties of dimethyl sulfate are listed in the following table.

Property	Information
Molecular weight	126.1 ^a
Density	1.33 g/mL at 20°C ^a
Melting point	-27°C ^a
Boiling point	188°C with decomposition ^a
Log <i>K</i> _{ow}	0.16 ^b
Water solubility	28 g/L at 18°C ^a
Vapor pressure	0.677 mm Hg at 25°C ^a
Vapor density relative to air	4.35 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Dimethyl sulfate is used primarily as a methylating agent to convert compounds such as phenols, amines, and thiols to the corresponding methyl derivatives (IARC 1999). It is also used as a methylating or sulfating agent in the manufacture of methyl esters, ethers, and amines in dyes, drugs, perfumes, pesticides, phenol derivatives, fabric softeners, polyurethane-based adhesives, and other organic chemicals. Dimethyl sulfate is also used as a solvent for the separation of mineral oils, for the analysis of auto fluids, and with boron to stabilize liquid sulfur trioxide (HSDB 2009). It was formerly used as a chemical weapon.

Production

Dimethyl sulfate has been produced commercially since at least the 1920s (IARC 1974, 1999). One production method is continuous reaction of dimethyl ether with sulfur trioxide (IARC 1974). In 2009, dimethyl sulfate was produced by 33 manufacturers worldwide, including 1 in the United States, 14 in China, 5 in India, 5 in Europe, 6 in East Asia, and 2 in Mexico (SRI 2009), and was available from 44 suppliers, including 16 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of dimethyl sulfate were found. Reports filed from 1986 through 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of dimethyl sulfate totaled 10 million to 50 million pounds (EPA 2004).

Exposure

The routes of potential exposure to dimethyl sulfate are inhalation, dermal contact, and ingestion (HSDB 2009). Dimethyl sulfate enters air and water largely through various waste streams resulting from its production and use. According to EPA's Toxics Release Inventory, environmental releases of dimethyl sulfate from 1988 to 2002 ranged from a high of 14,300 lb in 1989 to a low of 5,800 lb in 1993. Releases increased in 2003, primarily because a large quantity was released to air as fugitive emissions, mostly from a single facility. Since 2005, annual releases have totaled about 3,000 lb or less. In 2007, 2,626 lb of dimethyl sulfate was released to the environment from 11 facilities, primarily as air emissions (TRI 2009). Dimethyl sulfate released to air is likely to remain in the vapor phase and be degraded by reacting with the water in the atmosphere, with a half-life of over 30 min, or by reacting with photochemically produced hydroxyl radicals, with a half-life of over 32 days. Dimethyl sulfate is expected to hydrolyze in moist soils or surface water, with a half-life in water of 1.2 hours. The rapid hydrolysis rate in surface water prevents significant volatilization, adsorption to suspended solids or sediments, or biodegradation and bioconcentration. Dimethyl sulfate has been detected in remote rural air at a concentration of 58 ppt (299 ng/m³) and in urban air at concentrations almost a million times greater (several milligrams per cubic meter) (HSDB 2009).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 10,500 workers, including 2,500 women, potentially were exposed to dimethyl sulfate (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Dimethyl sulfate is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 500 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of dimethyl sulfate = U103, K131.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (5 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) (time-weighted-average workday) = 0.1 ppm (0.5 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 7 ppm.

Listed as a potential occupational carcinogen.

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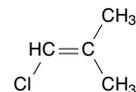
Dimethylvinyl Chloride

CAS No. 513-37-1

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as 1-chloro-2-methylpropene



Carcinogenicity

Dimethylvinyl chloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to dimethylvinyl chloride caused tumors in mice and rats at several different tissue sites. Administration of dimethylvinyl chloride by stomach tube caused forestomach cancer (squamous-cell carcinoma) in both sexes of both species, preputial-gland cancer (squamous-cell carcinoma) in male mice, nasal-cavity cancer (carcinoma and adenocarcinoma) in rats of both sexes, and oral-cavity cancer (squamous-cell carcinoma) in male rats. It also increased the combined incidence of benign and malignant tumors (squamous-cell papilloma and carcinoma) of the oral cavity in females and the esophagus in males (NTP 1986).

Since dimethylvinyl chloride was listed in the *Sixth Annual Report on Carcinogens*, one additional study in mice has been identified. In female Tg.AC mice (a transgenic mouse strain that carries the v-Ha-ras oncogene), exposure to dimethylvinyl chloride by stomach tube caused benign forestomach tumors (papilloma) (Cannon *et al.* 2000).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to dimethylvinyl chloride.

Properties

Dimethylvinyl chloride is a halogenated alkene that is a structural analogue of vinyl chloride monomer. It exists as a clear, colorless to brown liquid at room temperature (IARC 1995). It is slightly soluble in water, soluble in alcohol, ether, and acetone, and very soluble in chloroform. Dimethylvinyl chloride is flammable and polymerizes easily (Akron 2009). Physical and chemical properties of dimethylvinyl chloride are listed in the following table.

Property	Information
Molecular weight	90.6 ^a
Specific gravity	0.92 at 20°C/4°C ^a
Boiling point	68°C at 754 mm Hg ^a
Log K _{ow}	2.58 ^b
Water solubility	1 g/L at 25°C ^b
Vapor pressure	158 mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Dimethylvinyl chloride is not used commercially, but is used for research purposes. It has been used in organic syntheses and as a chemical intermediate for the production of isobutylene compounds for laboratory use (IARC 1995, HSDB 2009).

Production

Dimethylvinyl chloride is not produced for commercial use in the United States (HSDB 2009). In 2009, no commercial producers were identified worldwide, but dimethylvinyl chloride was available from seven suppliers, including four U.S. suppliers (ChemSources 2009). Dimethylvinyl chloride is a by-product in the production of 3-chloro-2-methylpropene from isobutylene (NTP 1986, HSDB 2009).

Exposure

Inhalation is the primary route of potential human exposure to dimethylvinyl chloride. In 1982, it was detected at concentrations ranging from 90 to 670 $\mu\text{g}/\text{m}^3$ in ambient-air samples collected near industrial complexes and chemical-waste-disposal sites (IARC 1995). In air, dimethylvinyl chloride will exist in the vapor phase and is expected to degrade with a half-life of about 21 hours by reaction with photochemically produced hydroxyl radicals or 26 hours by reaction with atmospheric ozone, or to be removed by wet deposition. In water, dimethylvinyl chloride is not expected to adsorb to sediment or to bioconcentrate, but is expected to volatilize rapidly, with a half-life of 2.9 hours in a model river and 3.8 days in a model lake. Dimethylvinyl chloride is expected to have high mobility in soil and to volatilize from either moist or dry soil.

Occupational exposure may occur during the production of 3-chloro-2-methylpropene, of which dimethylvinyl chloride is an unintended by-product. The U.S. Environmental Protection Agency estimated that 8 to 12 workers potentially were exposed to dimethylvinyl chloride during the production of 3-chloro-2-methylpropene (EPA 1985, HSDB 2009).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to dimethylvinyl chloride were identified.

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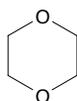
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1,4-Dioxane

CAS No. 123-91-1

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

1,4-Dioxane is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,4-dioxane caused tumors in several species of experimental animals and at several different tissue sites. Administration of 1,4-dioxane in drinking water caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes, female rats, and male guinea pigs. It also caused cancer of the nasal cavity (squamous-cell carcinoma) in rats of both sexes and gallbladder cancer (carcinoma) in male guinea pigs (IARC 1976, NCI 1978). In an initiation-promotion study, dermal exposure to 1,4-dioxane promoted the induction of skin tumors (squamous-cell carcinoma, sarcoma, and papilloma) by 7,12-dimethylbenzanthracene in mice of both sexes (IARC 1976).

Since 1,4-dioxane was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. 1,4-Dioxane administered in the drinking water increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in rats and mice of both sexes. In rats, it also caused nasal cancer (primarily squamous-cell carcinoma) and benign mammary-gland tumors (adenoma) in females and abdominal-cavity tumors (mesothelioma of the peritoneum) in males. Nasal tumors observed in male rats (squamous-cell carcinoma, esthesioneuropithelioma, rhabdomyosarcoma, and unspecified sarcoma) were considered to be exposure-related because of the rarity of these tumors (IARC 1999, Kano *et al.* 2009). As in the drinking-water studies, inhalation exposure of male rats to 1,4-dioxane caused benign liver tumors (hepatocellular adenoma), nasal cancer (squamous-cell carcinoma), and mesothelioma of the peritoneum. In addition, significant exposure-related trends were observed for tumors of the mammary gland (fibroadenoma), kidney (renal-cell carcinoma), and Zymbal gland (adenoma) (Kasai *et al.* 2009), although the incidences at the highest dose were not significantly higher than in the control group. In male strain A/J mice (a strain with a high spontaneous incidence of lung tumors), intraperitoneal injection of 1,4-dioxane increased the number of benign lung tumors (adenoma) per animal (Maronpot *et al.* 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,4-dioxane. A small prospective study of 165 U.S. workers exposed intermittently to low levels of 1,4-dioxane found no excess of death from cancer; however, the study was limited by the small number of cancer deaths (3) among the exposed workers (Buffler *et al.* 1978).

Properties

1,4-Dioxane (a dimer of ethylene oxide) is a cyclic ether that exists at room temperature as a colorless liquid with a faint, pleasant ethereal odor. It is miscible with water, oils, and most organic solvents, including aromatic hydrocarbons. 1,4-Dioxane is highly flammable and may form dangerous peroxides with prolonged exposure to air and sunlight, especially in the presence of moisture (IARC 1976, Akron 2009). Physical and chemical properties of 1,4-dioxane are listed in the following table.

Property	Information
Molecular weight	88.1 ^a
Specific gravity	1.03 at 20°C/4°C ^a
Melting point	12°C ^a
Boiling point	101°C ^a
Log K_{ow}	-0.27 ^b
Water solubility	1,000 g/L at 20°C ^b
Vapor pressure	37 mm Hg at 25°C ^a
Vapor density relative to air	3.03 ^a
Dissociation constant (pK_a)	-2.92 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

1,4-Dioxane is used as a solvent for cellulose acetate, ethyl cellulose, benzyl cellulose, resins, oils, waxes, and fats; in spectroscopic and photometric measurements; and in the pulping of wood. It is also used as a wetting and dispersing agent in textile processing, a degreasing agent, a polymerization catalyst, and a component of polishing compositions, dye baths, lacquers, paints, varnishes, stains, printing compositions, and paint and varnish removers (IARC 1976, 1999, ATSDR 2007, HSDB 2009). Other uses of 1,4-dioxane include the manufacture of adhesives, cements, deodorant fumigants, cosmetics, drugs, cleaning preparations, magnetic tape, plastic, rubber, insecticides, and herbicides, and as a chemical intermediate, as a polymerization catalyst, in the purification of drugs, and in the extraction of animal and vegetable oils. In the laboratory, it is used in the preparation of histological sections for microscopic examination and as a liquid scintillation counting medium. Historically, 90% of 1,4-dioxane was used as a stabilizer for 1,1,1-trichloroethane, typically at a concentration of 3.5% (ATSDR 2007). Because use of 1,1,1-trichloroethane has been limited under the Montreal Protocol on Substances that Deplete the Ozone Layer, this use is not expected to be significant.

Production

Commercial production of 1,4-dioxane in the United States was first reported in 1951, but semi-commercial quantities were available in 1929 (IARC 1976, ATSDR 2007). Estimated U.S. production of 1,4-dioxane was 12 million pounds in 1977 and 15 million pounds in 1982 (ATSDR 2007). In 2009, 1,4-dioxane was produced by one manufacturer each in the United States, Europe, and India and three manufacturers in East Asia (SRI 2009) and was available from 48 suppliers, including 26 U.S. suppliers (ChemSources 2009). From 1989 to 1995, U.S. imports of 1,4-dioxane fell from a high of 2.4 million pounds in 1989 to zero in 1995, while U.S. exports fluctuated between 11.9 million and 6.8 million pounds (USITC 2009). No more recent data on imports or exports were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,4-dioxane totaled 10 million to 50 million pounds in 1986 and 1990, decreasing to between 1 million and 10 million pounds between 1994 and 2006 (EPA 2004, 2009).

1,4-Dioxane may also be formed as a by-product during the manufacture of certain cosmetic ingredients, although it is not used as a cosmetic ingredient (FDA 2007).

Exposure

The routes of potential human exposure to 1,4-dioxane are inhalation, ingestion, and dermal contact. 1,4-Dioxane may be formed as a by-product of reactions based on condensing ethylene oxide or ethylene glycol during manufacture of detergents, shampoos, surfactants, some food additives (polysorbate 60 and polysorbate 80), and certain pharmaceuticals. The general population could be exposed to

1,4-dioxane through contact with residues contained in these products. Based on an analysis of the ingredients in 15,000 cosmetic and other personal-care products, 22% of all such products potentially contain 1,4-dioxane (EWG 2007). 1,4-Dioxane has also been reported to be present in other consumer products, such as adhesives and antifreeze products. Small amounts may be present in foods (such as meats and tomato juice), which may indicate that it is a natural constituent of some foods. It is also present in tap water, which means that exposure through the ingestion of drinking water, bathing, showering, and other household water uses are possible (ATSDR 2007).

Total environmental releases of 1,4-dioxane reported by EPA's Toxics Release Inventory from 1988 to 2009 ranged from 0.3 million to 1.3 million pounds (in 1993). In 2003, 53 facilities released 309,000 lb of 1,4-dioxane, of which 46% was released to air, 27% to surface water, and most of the remainder (26%) to off-site underground injection wells (TRI 2009). In air, 1,4-dioxane is expected to be subject to photooxidation, with a half-life of 1 to 3 days. It is expected to volatilize from water and soil. It adsorbs weakly to soil and sediment and will leach readily to groundwater. Because it does not undergo biodegradation, it will move rapidly through the subsurface with no significant change in concentration over time (Lesage *et al.* 1990). In groundwater, 1,4-dioxane forms the leading edge of a contaminant plume and travels much faster, farther, and more widely than other volatile organic compounds. However, it has a low potential for bioaccumulation. In 1984, the concentration of 1,4-dioxane in ambient air in the United States ranged from 0.1 to 0.4 $\mu\text{g}/\text{m}^3$, and the mean concentration in indoor air was 3.7 $\mu\text{g}/\text{m}^3$. In a 1990 study in California, the average indoor concentration of 1,4-dioxane was below the limit of quantitation (0.11 $\mu\text{g}/\text{m}^3$). In the United States, 1,4-dioxane was found in groundwater at concentrations ranging from less than 1 $\mu\text{g}/\text{L}$ to 109 $\mu\text{g}/\text{L}$ and in surface water at 1 $\mu\text{g}/\text{L}$ (ATSDR 2005).

Occupational exposure to 1,4-dioxane could occur during its production or its use as a solvent (IARC 1999). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 430,000 workers, including 149,697 women, potentially were exposed to 1,4-dioxane (NIOSH 1990). In 1968, the air concentration of 1,4-dioxane in the vicinity of storage tanks at three U.S. manufacturing facilities was as high as 800 ppm (2,883 mg/m^3). When these facilities were monitored in the mid 1970s, the concentrations of 1,4-dioxane measured in workplace air ranged from 0.2 to 22 ppm (0.7 to 79.3 mg/m^3). The maximum time-weighted-average occupational exposure concentrations were 16 ppm (57.6 mg/m^3) in production areas, 22 ppm (79.3 mg/m^3) in loading areas, 11 ppm (39.6 mg/m^3) around storage tanks, and 108.9 ppm (392.4 mg/m^3) for point-source emissions. Maximum personal monitoring samples ranged from 32 ppm (115.3 mg/m^3) for loading and control operators to 16.8 ppm (60.5 mg/m^3) for tank-car unloaders. Maximum concentrations in grab samples at measurement stations in the work area under normal operations ranged from 0.64 ppm (2.3 mg/m^3) to 1.5 ppm (5.4 mg/m^3); in one drum-filling and production area, the maximum concentration was 51 ppm (183.8 mg/m^3), and in another production area the maximum concentration was 36.7 ppm (132.2 mg/m^3) (NIOSH 1977, Santodonato 1985). Through 2005, five requests had been made to the National Institute for Occupational Safety and Health for health hazard evaluations of workplaces for exposure to 1,4-dioxane (Lewis 1979, Belanger 1980, Salisbury and Arnold 1984, Daniels 1987, Krake and Herrera-Moreno 1995). Two of these evaluations indicated excessive levels of 1,4-dioxane that contributed to adverse health effects in the workers, and changes in the work environment were recommended.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,4-dioxane on ships and barges.

Department of Transportation (DOT)

1,4-Dioxane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,4-dioxane = U108.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

1,4-Dioxane levels shall not exceed 10 mg/kg in glycerides and polyglycerides of hydrogenated vegetable oils when used as a food additive.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 100 ppm (360 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 20 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Ceiling recommended exposure limit = 1 ppm (3.6 mg/m³) (30-min exposure).

Immediately dangerous to life and health (IDLH) limit = 500 ppm.

Listed as a potential occupational carcinogen.

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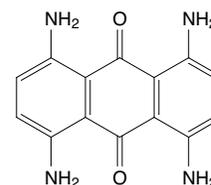
Disperse Blue 1

CAS No. 2475-45-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as C.I. disperse blue 1, C.I. 64500, or 1,4,5,8-tetraaminoanthraquinone



Carcinogenicity

Disperse blue 1 is *reasonably anticipated to be a human carcinogen* based on (1) sufficient evidence of carcinogenicity from studies in experimental animals and (2) the fact that it belongs to a well-defined, structurally related class of anthraquinones whose members are listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens*.

Cancer Studies in Experimental Animals

Oral exposure of rats to disperse blue 1 caused tumors of a type that is rare in this species. Dietary administration of disperse blue 1 caused benign and malignant urinary-bladder tumors in rats of both sexes (Burnett and Squire 1986, NTP 1986). Incidences were significantly increased of benign and malignant transitional-cell tumors combined (papilloma and carcinoma) and malignant tumors of the smooth muscle and smooth-muscle connective tissue combined (leiomyoma and leiomyosarcoma) in both sexes, as well as benign and malignant squamous-cell tumors combined (papilloma and carcinoma) in females. No urinary-bladder tumors were observed in any of the concurrent control groups. The historical control incidence of urinary-bladder tumors was 0.3% in males (6 tumors in 2,189 animals) and 0.2% in females (5 tumors in 2,263 animals); the tumors included 6 transitional-cell papillomas, 2 transitional-cell carcinomas, 1 leiomyoma, and 2 papillomas not otherwise specified. The findings in mice orally exposed to disperse blue 1 were equivocal, based on marginally increased combined incidences of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) and lung tumors (alveolar/bronchiolar adenoma and carcinoma).

Studies on Mechanisms of Carcinogenesis

In genotoxicity studies of anthraquinone derivatives and related anthracene derivatives, 35% of the compounds tested have shown some mutagenic activity. Of the anthraquinone analogues tested, mutagenic activity was strongest for nitro-anthraquinones, followed by hydroxy-anthraquinones, and was weakest for amino-anthraquinones; all nitro-anthraquinones tested were mutagenic. Disperse blue 1 was weakly mutagenic in *Salmonella typhimurium* (Brown and Brown 1976). It also caused sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells (Anderson *et al.* 1990), *tk* gene mutations in mouse lymphoma L5178Y cells (Myhr *et al.* 1990), and morphological transformation in Balb/c 3T3 mouse cells (Matthews *et al.* 1993).

A study of the relationship between chemical structure and the carcinogenic activity of anthraquinone and six anthraquinone derivatives tested in long-term bioassays found that changes in functional groups (i.e., amino-, alkyl-, nitro-, hydroxyl-, or halogen substitutions) altered the tissue sites of carcinogenesis, which included liver, kidney, skin, intestine, and urinary bladder in rats, and liver, skin, forestomach, and lung in mice (Doi *et al.* 2005).

The occurrence of urinary-bladder tumors (transitional- and squamous-cell tumors) in rats exposed to disperse blue 1 was associated with the dose-dependent incidence of calculi, which were thought to cause chronic inflammation and cell proliferation (NTP 1986). Calculi and resulting inflammatory and proliferative lesions also occurred in the urinary bladder of mice of both sexes, although tumor incidences were not significantly increased. It has been suggested that urinary-bladder calculi do not appear to form in humans at normal levels of exposure to disperse blue 1 (CIR 1995). However, there is no compelling evidence for a causal relationship between urinary-bladder calculi and development of leiomyoma or leiomyosarcoma in rats to contradict the evidence that disperse blue 1 is *reasonably anticipated to be a human carcinogen*.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to disperse blue 1.

Properties

Disperse blue 1 is an amino-anthraquinone-based dyestuff (NTP 1986) that exists at room temperature as a blue-black microcrystalline powder. It is practically insoluble in water, soluble in acetone, ethanol, and cellosolve (glycol ether), and slightly soluble in benzene and linseed oil. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of disperse blue 1 are listed in the following table.

Property	Information
Molecular weight	268.3 ^a
Melting point	332°C ^a
Log K_{ow}	-0.96 ^a
Water solubility	0.03 mg/L at 25°C ^b
Vapor pressure	1.8×10^{-8} mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Disperse blue 1 has been used in hair-color formulations and to color fabrics and plastics. Commercial preparations of disperse blue 1 contain approximately equal amounts of dyestuff and lignosulfonate dispersants. In the mid 1980s, it was reported that semi-permanent hair-color formulations commonly contained disperse blue 1 at concentrations of less than 1% (NTP 1986). Disperse blue 1 is used as a fabric dye for nylon, cellulose acetate and triacetate, polyester, and acrylate fibers and for surface dyeing of thermoplastics, as a solvent dye in cellulose acetate plastics, and to dye fur and sheepskins (NTP 1986, IARC 1990, HSDB 2009). It is also used in some personal-care products, such as hair mousse and toothpaste (HPD 2009).

Production

The last reported quantity for U.S. production of disperse blue 1 was over 350,500 lb in 1972 (IARC 1990); after 1972, production figures specifically for disperse blue 1 were no longer reported. Production in the United States, by one company, was last reported in 1992 (HSDB 2009). In 2009, no commercial manufacturers of disperse blue 1 were identified worldwide (SRI 2009), but disperse blue 1 was available from five suppliers, including three U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of disperse blue 1 were found.

Exposure

The routes of potential human exposure to disperse blue 1 are inhalation, ingestion, and dermal contact (HSDB 2009). Ingestion is a potential route of exposure because of the use of disperse blue 1 in toothpaste. More commonly, it is used in hair dyes or hair mousse, and individuals using, producing, or applying these products potentially could be exposed by inhalation and dermal contact (IARC 1990). In the mid 1980s, it was reported that over 3 million people in the United States used semipermanent hair-color preparations containing disperse blue 1, usually at concentrations of less than 1% (NTP 1986). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 43,522 workers (mostly in the Personal Services industry), including 32,059 women, potentially were exposed to disperse blue 1 (NIOSH 1990).

Environmental releases can occur from production or use of disperse blue 1. If released to air, disperse blue 1 will exist mainly as a particulate, and it is not expected to be volatile in soil or water. It is estimated to have low mobility in soil and will bind to soil and water sediments. Based on estimated bioconcentration factors, disperse blue 1 may bioaccumulate in aquatic organisms (HSDB 2009).

Regulations

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

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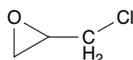
Epichlorohydrin

CAS No. 106-89-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as 1-chloro-2,3-epoxypropane or CEP



Carcinogenicity

Epichlorohydrin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Epichlorohydrin caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In male rats, administration of epichlorohydrin by stomach tube caused be-

nign and malignant tumors of the forestomach (carcinoma and papilloma), and inhalation exposure to epichlorohydrin caused benign and malignant tumors of the nasal cavity (carcinoma and papilloma). In female mice, epichlorohydrin administered by subcutaneous injection caused cancer at the injection site (sarcoma). Epichlorohydrin applied to the skin acted as an initiator in a tumor initiation-promotion study in female mice, but did not cause tumors when applied alone (IARC 1976).

Since epichlorohydrin was listed in the *Fourth Annual Report on Carcinogens*, additional studies in rodents have been identified. Administration of epichlorohydrin by stomach tube caused cancer of the forestomach (carcinoma) in rats of both sexes (Wester *et al.* 1985, IARC 1999). In male strain A/J mice (a strain with a high spontaneous incidence of lung cancer), epichlorohydrin administered by intraperitoneal injection increased the number of lung tumors per animal (Stoner *et al.* 1986, IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to epichlorohydrin. One cohort study of workers exposed to epichlorohydrin at two factories found a significant excess of respiratory cancer; however, some of the workers had been engaged in the manufacture of isopropyl alcohol and may have been exposed to diisopropyl sulfate (Enterline 1982, IARC 1982).

Since epichlorohydrin was listed in the *Fourth Annual Report on Carcinogens*, the International Agency for Research on Cancer has reviewed its carcinogenicity twice (IARC 1987, 1999). The 1999 review included a follow-up study of the cohort exposed to epichlorohydrin and isopropyl alcohol (Enterline 1982), as well as additional cohort and nested case-control studies. No excess of lung cancer was observed in the follow-up study (Tsai *et al.* 1996), in a small cohort of workers exposed to epichlorohydrin and allyl chloride (Olsen *et al.* 1994), or in a nested case-control study of male chemical workers (Bond *et al.* 1986). A cohort study of resin and dye makers found a significant excess of lung cancer, but a nested case-control study of lung cancer in this cohort found no association with exposure duration or cumulative exposure level (Delzell *et al.* 1989). A nested case-control study of nervous-system cancer in the same cohort found a statistically nonsignificant excess of central nervous system cancer; risk increased with both exposure duration ($P_{\text{trend}} = 0.11$) and cumulative exposure level ($P_{\text{trend}} = 0.08$). These studies were limited by small sample sizes, co-exposure of workers to other substances, and lack of control for potentially confounding variables. IARC (1999) concluded that there was inadequate evidence in humans for the carcinogenicity of epichlorohydrin.

Properties

Epichlorohydrin is an epoxide with bifunctional alkylating activity which at room temperature exists as a colorless liquid with a sweet, pungent, chloroform-like odor. It is soluble in water and benzene, miscible with ethanol, diethyl ether, chloroform, trichloroethylene, and carbon tetrachloride, and immiscible with petroleum hydrocarbons (IARC 1999). Epichlorohydrin is stable at normal temperature and pressure, but is highly flammable with moderate heating (Akron 2009). It can react violently with chemicals carrying an active hydrogen atom, including water (IARC 1999, HSDB 2009). It is heavier than air and may travel from its source and collect in low-lying areas (HSDB 2009). Physical and chemical properties of epichlorohydrin are listed in the following table.

Property	Information
Molecular weight	92.5 ^a
Specific gravity	1.18 at 25°C/4°C ^a
Melting point	-26°C ^a
Boiling point	118°C ^a
Log K_{ow}	0.45 ^a
Water solubility	66 g/L at 25°C ^b
Vapor pressure	16.4 mm Hg at 25°C ^a
Vapor density relative to air	3.3 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Epichlorohydrin is used in the production of numerous synthetic materials, including epoxy, phenoxy, and polyamide resins, polyether rubber used in car parts, synthetic glycerin, glycidyl ethers, polythiols, elastomers, cross-linked food starch, surfactants, plasticizers, dyestuffs, pharmaceutical products, oil emulsifiers, lubricants, and adhesives (IARC 1976, WHO 1984). Epichlorohydrin may be used as a homopolymer or copolymer in the synthesis of epichlorohydrin rubber (Machine Design 2007). It is also used as a solvent for resins, gums, cellulose, esters, paints, and lacquers; to cure propylene-based rubbers; and in resins with high wet strength for the paper industry (IARC 1976, 1999). Epichlorohydrin is widely used as a stabilizer in chlorine-containing substances such as rubber, pesticide formulations, and solvents (HSDB 2009).

Production

Epichlorohydrin was first synthesized in 1854. Small-scale production in the United States began in 1937, and large-scale production in 1949. From 1973 to 1978, production ranged from 157 million kilograms (346 million pounds) to 250 million kilograms (551 million pounds) (IARC 1976, 1999). In 2009, epichlorohydrin was produced by 27 manufacturers worldwide, including 2 in the United States, 9 in East Asia, 6 in Europe, 8 in China, 1 in India, and 1 in the Middle East (SRI 2009), and was available from 50 suppliers, including 27 U.S. suppliers (ChemSources 2009). From 1989 to 2008, U.S. exports of epichlorohydrin ranged from a low of 15.8 million kilograms (34.8 million pounds) in 1992 to a high of 136 million kilograms (300 million pounds) in 2006; in 2008, exports were 81.9 million kilograms (180.6 million pounds) (USITC 2009). Over the same period, U.S. imports ranged from a low of 2.0 million kilograms (4.4 million pounds) in 1994 to a high of 19.1 million kilograms (42.1 million pounds) in 2000. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule from 1986 to 2002 indicated that U.S. production plus imports of epichlorohydrin totaled over 500 million pounds; in 1998, the reported quantity exceeded 1 billion pounds (EPA 2004).

Exposure

The routes of potential human exposure to epichlorohydrin are ingestion, inhalation, and dermal contact (HSDB 2009). Evidence suggests that epichlorohydrin is readily absorbed when ingested or inhaled and that it is a systemic poison when absorbed through the skin (WHO 1984). Exposure will occur primarily in occupational settings, but individuals in the general population may be exposed while using epoxy resins (Howard 1989) or through ingestion of food (WHO 1984, FDA 2010a,b,c,d,e). Food may contain epichlorohydrin as a result of its use as a cross-linker in modified food starch and in food processing or in food packaging materials, such as adhesives and coatings. Concentrations of epichlorohydrin in modified food starch are required to be below 0.3%, which limits the potential daily intake through ingestion.

According to EPA's Toxics Release Inventory, 45 facilities released a total of 155,878 lb of epichlorohydrin to the environment in 2007, of which 84% was released to air, 6% to surface water, and most of the remaining 10% to on- and off-site landfills (TRI 2009). Reported epichlorohydrin releases have declined continuously from a high of almost 909,000 lb in 1989, of which 77% was released to air, 1% to surface water, 22% to underground injection wells, and virtually none to landfills. Over time, the amount of epichlorohydrin released to land has increased, while total releases and releases to air have declined, and releases to surface water and underground injection wells have fluctuated. Epichlorohydrin has been detected, but not quantified, in surface water and river sediment (HSDB 2009). Epichlorohydrin was also released to the environment as a result of two railroad accidents in West Virginia; in 1963, 5,000 gal was released into the New River at South Fayette, and in 1978, 20,000 gal was released near the center of the town of Point Pleasant. In the latter instance, contamination of groundwater was confirmed; epichlorohydrin was found at a concentration of 75 ppm in the well closest to the spill site.

When released to air, epichlorohydrin will be degraded by photochemically produced hydroxyl radicals, with an estimated half-life of 4 days. If released to surface water, epichlorohydrin is expected not to adsorb to sediment, but to volatilize, with an estimated half-life of 19 hours in a model river and 12 days in a model lake (HSDB 2009). Hydrolysis is expected to occur with a half-life of 8.2 days in distilled water and 5.3 days in seawater. Hydrolysis will produce 3-chloro-1,2-propanediol in fresh water and 1,3-dichloro-2-propanol in seawater (Howard 1989). If epichlorohydrin is spilled on land, it most likely will volatilize or leach into the subsurface; biodegradation and hydrolysis also may occur in soil. Bioaccumulation in aquatic organisms is unlikely (HSDB 2009).

Occupational exposure may occur during the production of epichlorohydrin and during its use to synthesize end products. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 85,000 workers in 10 industry segments potentially were exposed to epichlorohydrin (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 80,170 workers in 24 industry segments, including 14,921 women, potentially were exposed (NIOSH 1990).

Studies of occupational exposure to epichlorohydrin have been conducted for the chemical and paper-manufacturing industries and at resin and synthetic leather manufacturing plants (Kuo *et al.* 2000, Luo *et al.* 2003, 2004, Korhonen *et al.* 2004). Comprehensive industrial surveys conducted for the National Institute for Occupational Safety and Health between 1973 and 1976 at seven facilities manufacturing epichlorohydrin, epoxy resins, and glycerol suggested that chemical operators at these plants had the greatest potential for exposure to epichlorohydrin. Time-weighted-average (TWA) exposure concentrations ranged from less than 0.04 to 7.9 mg/m³. In two other epoxy resin manufacturing facilities, the TWA concentration of epichlorohydrin was generally below 3.8 mg/m³. Concentrations in the laboratory areas of these plants were higher, ranging from 3.8 to 18.9 mg/m³ (WHO 1984). In a solvent epichlorohydrin production plant, concentrations were as high as 5.5 ppm (20.8 mg/m³) during normal production and 54.9 ppm (207.5 mg/m³) when there were mechanical difficulties (Howard 1989). As of 2005, health hazard evaluations had been requested by workers in 10 facilities based at least in part on epichlorohydrin exposure; however, the NIOSH investigations resulted in a recommendation for workplace practice changes at only one facility (a wet corn milling facility), based on an epichlorohydrin concentration of 0.1 mg/m³ (Ferguson 1977, Lewis 1979, Markel 1979, Chrostek and Levine 1980, McGlothlin *et al.* 1980, Stephenson *et al.* 1981, Lee *et al.* 1982, Liss and Ruhe 1982, Lee 1985, Hills 1988).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of epichlorohydrin on ships and barges.

Department of Transportation (DOT)

Epichlorohydrin is considered a hazardous material and a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture or use of epichlorohydrin is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity = 20,000 lb.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 1,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of epichlorohydrin = U041, K017.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Each public water system must certify annually that when epichlorohydrin is used in drinking water systems, the level does not exceed 0.01% dosed at 20 ppm (or equivalent).

Food and Drug Administration (FDA)

Food starch may be etherified or esterified by treatment with epichlorohydrin, with maximum epichlorohydrin levels ranging from 0.1% to 0.3% (depending on process).

Various epichlorohydrin copolymers may be used as food additives and food contact materials as prescribed in 21 CFR 172, 173, 175-178.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 5 ppm (19 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 75 ppm.

Listed as a potential occupational carcinogen.

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Erionite

CAS No. 66733-21-9

Known to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)

Carcinogenicity

Erionite is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Descriptive studies have reported an excess of mortality from mesothelioma (cancer of body cavity linings) in individuals living in three villages in Turkey where there was chronic exposure to erionite (IARC 1987a,b, Baris 1991). No cases of mesothelioma occurred in a control village without exposure to erionite. An excess of lung cancer also was reported in two of the three villages contaminated with erionite. Respirable erionite fibers were detected in air samples collected from the contaminated villages, and lung tissue samples collected from individuals with mesothelioma contained erionite fibers. In another study, a higher proportion of ferruginous (iron-containing) bodies with a zeolite core were found in inhabitants of two contaminated villages than in inhabitants of two control villages.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of erionite from studies in experimental animals. High incidences of mesothelioma were observed in rats exposed to erionite by inhalation or by intrapleural or intraperitoneal injection and in mice exposed by intraperitoneal injection (IARC 1987a,b).

Properties

Erionite is a naturally occurring fibrous mineral that belongs to a group of minerals called zeolites. Zeolites are hydrated aluminosilicates of the alkaline and alkaline-earth metals, and erionite is one of the more common of the approximately 40 natural types identified (Virta 2002). It has a hexagonal, cage-like structure composed of a framework of linked (Si,Al)O₄ tetrahedra. The structure is chainlike, with six tetrahedra on each edge of the unit forming part of a chain of indefinite length. It consists of white prismatic crystals in radiating groups and occurs in a fibrous form. Erionite absorbs up to 20% of its weight in water, has a specific gravity of 2.02 to 2.08, and has gas absorption, ion exchange, and catalytic properties that are highly selective and depend on the molecular size of the sorbed compounds (IARC 1987a). Zeolites, in general, have good thermal stability, rehydration kinetics, and water vapor adsorption capacity (Clifton 1985).

Use

Erionite is no longer mined or marketed for commercial purposes. Although other natural zeolites have many commercial uses (e.g., in

pet litter, soil conditioners, animal feed, wastewater treatment, or gas absorbents) because of their unique properties, very few data are available specifically for erionite. It reportedly was used in the past as a noble-metal-impregnated catalyst in a hydrocarbon-cracking process and was studied for use in fertilizers and to control odors in livestock production. Erionite-rich blocks have been used to build houses in parts of the western United States, but this was a minor and unintentional use of the mineral (IARC 1987a).

In 1999, natural zeolites were described as “full-fledged mineral commodities” with promise for expanded use in the future (Mumpton 1999). In 2001, the global annual consumption of natural zeolites was estimated to be 3.98 million metric tons (8.8 billion pounds), and the market was projected to grow to 5.5 million metric tons (12.1 billion pounds) per year by 2010 (Frost and Sullivan 2000). Most commercial uses of natural zeolites are based on their ability to selectively adsorb molecules from air or liquids (IARC 1987a). Domestic uses for natural zeolites in 2002 were, in decreasing order by tonnage, pet litter, animal feed, horticultural applications (use as soil conditioners and growth media), miscellaneous applications, oil absorbent, odor control, desiccant, pesticide carrier, water purification, aquaculture, wastewater cleanup, gas absorbent, and catalyst (Virta 2002). Pet litter, animal feed, and horticultural applications accounted for more than 65% of domestic sales tonnage. The largest increases in tonnage sales were for use in animal feed and pet litter.

Production

Commercial mining of ores containing erionite by two U.S. companies began in the 1960s and continued through the 1970s (IARC 1987a). During that time, erionite was one of four commercially important zeolites (Mumpton 1978, Kresge and Dhingra 2004). By 2002, nine companies were mining natural zeolites in the United States (Virta, 2002). Zeolite minerals are associated with the alteration of volcanic tuffs in saline lake water. Several hundred occurrences of zeolite deposits have been recorded in over 40 countries. Commercial deposits in the United States are in Arizona, California, Idaho, Nevada, New Mexico, Oregon, Texas, Utah, and Wyoming. Erionite occurs in rocks of many types and in many geologic settings; however, it rarely occurs in pure form and normally is associated with other zeolite minerals. In several locations, however, erionite exists in deposits exceeding millions of tons (IARC, 1987).

No production data specifically for erionite were available; however, commercial mining of other natural zeolites continues. Only a few hundred tons of zeolites were mined annually in the United States through the 1970s, and by the mid 1980s, annual production was still less than 10,000 metric tons (22 million pounds). U.S. production then started to increase, peaking in 1994 at 52,800 metric tons (116 million pounds) (Virta 2000). In 2002, nine companies reported mining 46,000 metric tons (101 million pounds) of zeolites, up from 36,400 metric tons (80 million pounds) reported in 2001 (Virta 2002).

Exposure

Zeolites are one of the most extensive mineral families in the earth's crust (Vaughan 1978). Fibrous and nonfibrous zeolites are common minerals in the western United States; there are 10 trillion tons of reserves, and 120 million tons exist near the surface of the ground (Rom *et al.* 1983). The zeolite beds may be up to 15 feet thick and may lie in surface outcroppings. Deposits of fibrous erionite are located in Arizona, Nevada, Oregon, and Utah. Erionite fibers have been detected in samples of road dust in Nevada. U.S. residents of the Intermountain West may potentially be exposed to fibrous erionite in ambient air (Rom *et al.* 1983, IARC 1987a).

Potential occupational exposure to erionite occurs during the production and mining of other zeolites. In the past, occupational exposure occurred from erionite mining and production operations. Erionite was also reported to be a minor component in some other commercial zeolites (Mondale *et al.* 1978). Therefore, the use of other zeolites may result in potential exposure to erionite for workers and members of the general population who use the zeolites in a variety of processes and products. Total dust exposures for miners in an open-pit zeolite mine that contained some erionite in Arizona ranged from 0.01 to 13.7 mg/m³; respirable dust in the mining area was 0.01 to 1.4 mg/m³ (IARC 1987a).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to erionite were identified

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Estrogens, Steroidal

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Introduction

Steroidal estrogens are cholesterol derivatives comprising a group of structurally related, hormonally active molecules that control sex and growth characteristics. The National Toxicology Program previously evaluated some specific steroidal estrogens, including conjugated estrogens (listed in the *Fourth Annual Report on Carcinogens* in 1985 as *known to be human carcinogens*) and a number of individual nonconjugated steroidal estrogens, including estradiol-17 β , estrone, ethinylestradiol, and mestranol (which also were listed in the *Fourth Annual Report on Carcinogens* in 1985 as *reasonably anticipated to be human carcinogens*). In identifying steroidal estrogens as carcinogenic to humans, the International Agency for Research on Cancer noted that its evaluation applied to the group of chemi-

cals as a whole and not necessarily to all individual chemicals within the group (IARC 1987).

This listing of steroidal estrogens supersedes the previous listings of steroidal estrogens and conjugated estrogens in the Report on Carcinogens and applies to all chemicals of this steroid class. The profile for steroidal estrogens includes information on carcinogenicity, properties, use, production, exposure, and regulations for steroidal estrogens as a class, as well as some specific information for individual estrogens.

Carcinogenicity

Steroidal estrogens are *known to be human carcinogens* based on sufficient evidence of carcinogenicity in humans.

Cancer Studies in Humans

Human epidemiological studies have shown that the use of estrogen replacement therapy by postmenopausal women is associated with a consistent increase in the risk of uterine endometrial cancer and a less consistent increase in the risk of breast cancer. Some evidence suggests that oral contraceptive use also may increase the risk of breast cancer.

IARC (1999) evaluated the carcinogenic effects of estrogen replacement therapy used to relieve symptoms of menopause and reported that an increased risk of endometrial cancer was associated with increasing duration of estrogen therapy, as well as a small increased risk of breast cancer. Studies since the IARC review have supported these findings. Four studies (one cohort study and three large case-control studies) reported increased risk of endometrial cancer with estrogen replacement therapy (Cushing *et al.* 1998, Shapiro *et al.* 1998, Persson *et al.* 1999, Weiderpass *et al.* 1999), and three of these studies reported strong positive associations between risk of endometrial cancer and duration of estrogen use. Three cohort studies of women taking either estrogen replacement therapy or hormone replacement therapy (estrogen and progestogen combined) found an association with breast cancer (Gapstur *et al.* 1999, Persson *et al.* 1999, Schairer *et al.* 2000). Two of four case-control studies found that estrogen-only replacement therapy was associated with an increased risk of breast cancer (Heinrich *et al.* 1998, Magnusson *et al.* 1999), whereas a third study reported a slight reduction in breast-cancer risk among women receiving estrogen replacement therapy (Brinton *et al.* 1998), and a fourth found no association of breast-cancer risk with hormone replacement therapy (Titus-Ernstoff *et al.* 1998). One study found that estrogen therapy was associated with ovarian cancer (Purdie *et al.* 1999).

IARC (1999) also evaluated cancer risks associated with the use of oral contraceptives. Most of these studies involved estrogen-progestogen combinations. In general, oral contraceptive use was associated with a small increased risk of breast cancer. Three case-control studies published after the IARC evaluation did not find an increased risk of breast cancer with oral contraceptive use (Brinton *et al.* 1998, Titus-Ernstoff *et al.* 1998, Rohan and Miller 1999). Other studies indicated that oral contraceptive use might decrease the risk of ovarian and endometrial cancer (Salazar-Martinez *et al.* 1999), confirming the results of studies reviewed by IARC.

Since steroidal estrogens were listed in the *Tenth Report on Carcinogens*, additional epidemiological studies have been identified. These studies reported an increased risk of endometrial cancer among women using estrogen-only therapy, supporting the findings of earlier studies (Epstein *et al.* 2009), and less consistent findings for breast cancer in case-control studies of estrogen-only menopausal therapy (Prentice *et al.* 2008a, 2009, Calle *et al.* 2009, Jick *et al.* 2009). In 2009, IARC concluded there was sufficient evidence of the carcinogenic-

ity of estrogen-only therapy in humans based on increased risks of endometrial cancer and ovarian cancer and limited evidence based on increased risk of breast cancer (Grosse *et al.* 2009). The findings for ovarian cancer were based on two meta-analyses (Greiser 2007, Zhou 2008). Since then, another meta-analysis has estimated a significant overall increase in ovarian cancer risk related to duration of use of estrogen-only therapy (Pearce *et al.* 2009).

Since estrogen-only oral contraceptives were phased out starting in the mid 1970s, most of the studies of oral contraceptive use have involved estrogen-progestogen combinations. In subsequent reviews, IARC concluded that there was sufficient evidence of the carcinogenicity of combination oral contraceptives in humans based on increased risks of breast, cervical, and liver cancer (IARC 2007) and sufficient evidence for the carcinogenicity of combined estrogen-progestogen menopausal therapy in humans based on increased risk of breast cancer (Grosse *et al.* 2009). The results of studies published since the 2007 review were consistent with the conclusions of the IARC review, finding increased risk of breast cancer associated with both oral contraceptive use (Rosenberg *et al.* 2009) and estrogen-progestogen menopausal therapy (Prentice *et al.* 2008b, 2009, Calle *et al.* 2009, Chlebowski *et al.* 2009, Jick *et al.* 2009, Lyytinen *et al.* 2009). In both reviews, IARC also noted that a lower risk of endometrial cancer was associated with oral contraceptive use. The 2009 IARC review concluded that the risk of endometrial cancer associated with menopausal therapy decreased with increasing duration of progestogen use. In two large studies of endometrial cancer, combination therapy reduced the increase in risk of endometrial cancer associated with estrogen-only therapy in women with higher body mass index (McCullough *et al.* 2008, Epstein *et al.* 2009). A reanalysis of cervical-cancer cases from over 20 studies found an increased risk among current oral contraceptive users (Appleby *et al.* 2007), supporting the results of the IARC review. The IARC reviews and a reanalysis of 45 epidemiological studies (Beral *et al.* 2008) found that oral contraceptive use was associated with a decreased risk of ovarian cancer.

Cancer Studies in Experimental Animals

In rodents, steroidal estrogens caused benign and malignant tumors, as well as pre-cancerous lesions, in a variety of organs, including the mammary gland and female reproductive tract (IARC 1999). The strength of evidence in experimental animals differed among various estrogenic compounds. Estrogenic compounds generally caused endometrial, cervical, and mammary-gland tumors in mice, mammary- and pituitary-gland tumors in rats, and kidney tumors in hamsters.

Studies on Mechanisms of Carcinogenesis

Although there is no evidence of genotoxic effects in nonmammalian test systems, some steroidal estrogens can damage mammalian DNA and chromosomes (IARC 1999). The most frequently reported effects included DNA adduct formation, cytogenetic alterations (e.g., chromosome and chromatid breaks, micronucleus formation, and sister chromatid exchange), and aneuploidy. Most of these effects were demonstrated in various tests using animal cells or cell-free systems. Studies with cultured human cell lines showed evidence of aneuploidy, DNA strand breaks, micronucleus formation, and sister chromatid exchange. No data were found on genetic effects of steroidal estrogens in humans *in vivo*.

Among mammals, including humans, metabolism is essentially similar for three naturally occurring unconjugated estrogens: estradiol, estrone, and estriol are metabolized via similar phase I pathways (aromatic hydroxylation to catechol intermediates) and phase II pathways (glucuronidation, sulfonation, and O-methylation). The distri-

bution of metabolic products depends on the target tissue, species, strain, sex, and experimental conditions (IARC 1999).

The evidence is strong that estrogen carcinogenesis is mediated through activation of the estrogen receptor. In addition, there is evidence that other mechanisms may play a role in the carcinogenic effects of estrogens in some tissues. For example, prolonged estrogen exposure causes cell proliferation in estrogen-dependent target cells, affects cellular differentiation, and alters gene expression. Although the molecular mechanisms responsible for estrogen carcinogenicity are not understood, the evidence indicates that estrogen carcinogenesis is complex, involving proliferative effects and possibly direct and indirect genotoxic effects. The relative importance of each mechanism is likely a function of the specific estrogen and of the exposed tissue or cell type and its metabolic state (Yager and Liehr 1996).

Properties

Steroidal estrogens comprise a group of structurally related hormone molecules derived from the cholesterol molecule (IARC 1979a). Estrogens are found in males and females, and are the primary sex hormones in females. Steroidal estrogens are fat-soluble (lipophilic) molecules that are essential for the growth, differentiation, and function of tissues in humans and other vertebrate animals. "Estrogen" is a collective term for the naturally occurring female hormones estradiol, estriol, and estrone. In females, estrogen is important in the development of secondary sexual characteristics, in the regulation of the menstrual cycle, and in pregnancy. In males, estrogen is important in the maturation of sperm. Estrogen also plays an important role in normal bone development and maintenance in both males and females. In the brain, estrogen affects factors regulating procreation, including reproductive behavior, mood, and production and release of gonadotropins from the pituitary.

Both naturally occurring estrogens (e.g., estrone and estradiol-17 β) and synthetic estrogens (e.g., mestranol and ethinylestradiol) are widely used medicinal drugs. Estradiol-17 β occurs as an odorless, white or creamy-white crystalline powder with a molecular weight of 272.4 and a melting point of 173°C to 179°C (IARC 1979b, 1999). Estrone is an odorless, white to creamy-white crystalline powder with a molecular weight of 270.4 and a melting point of 254.5°C to 256°C. Estriol exists as very small, monoclinic crystals with a molecular weight of 288.4 and a melting point of 282°C.

Conjugated estrogens are a noncrystalline mixture containing naturally occurring forms of mixed estrogens, principally sodium estrone sulfate and sodium equilin sulfate. Piperazine estrone sulfate is a synthetic conjugated estrogen. Conjugated estrogens generally occur as odorless, buff-colored powders that are soluble in water. Nonconjugated estrogens (both naturally occurring and synthetic) are practically insoluble in water but slightly soluble to soluble in organic solvents (e.g., ethanol, acetone, diethyl ether, and chloroform). Mestranol is a white crystalline powder with a molecular weight of 310.4 and a melting point of 150°C to 151°C. Ethinylestradiol occurs as an odorless, creamy or yellowish-white crystalline powder with a molecular weight of 296.4 and a melting point of 182°C to 184°C for the more stable form and 141°C to 146°C for the less stable form.

Use

Estradiol-17 β is the predominant estrogen in non-pregnant women, and estriol is the primary estrogen produced during pregnancy. Estradiol-17 β and its metabolite estrone are secreted by the ovaries in women with normal menstrual cycles and by the placenta in pregnant women. They both are essential for growth and normal maintenance of the lining of the uterus, for development of the accessory and secondary female sex characteristics, and for pregnancy (Prosser 1973).

Conjugated estrogens, estradiol, and synthetic esters of estradiol, especially ethinylestradiol and estradiol valerate, are most commonly used for estrogen-replacement therapy or in combination with a progestogen for hormone-replacement therapy. Unopposed estrogens, as commonly prescribed in the 1960s and 1970s, were shown to cause endometrial cancer; however, addition of a progestogen greatly diminished that risk (Loose-Michael and Stancel 2001). These replacement therapies are used to treat symptoms of menopause, including menopause surgically induced by removing the ovaries. Estrogens are used to prevent the sweating episodes called “hot flashes” and the shrinking and irritation that sometimes occur in the vulva, vagina, and urinary tract during menopause. Estrogens can be used to prevent common postmenopausal conditions such as osteoporosis and ischemic heart disease and have been shown to decrease the rate of colorectal cancer. They also have been used to treat low estrogen levels (hypoestrogenism) in males and females caused by hypogonadism, castration, or primary ovarian failure (IARC 1999, HSDB 2009).

Estrogens have been used in oral contraceptives since the early 1960s. Steroidal estrogens, most commonly ethinylestradiol, are also used with various progestogens in combined oral contraceptive formulations. Currently, many of the oral contraceptives used in the United States contain either 30 or 35 µg of ethinylestradiol, because this dose has contraceptive efficacy, is well tolerated, and has a low risk of side effects (e.g., such adverse events as breakthrough bleeding) (Schwend and Lippman 1996). Mestranol is available only in combination with progestogens and is used in typical estrogen therapies, particularly in some oral contraceptive formulations. Combined oral contraceptives typically are administered as a pill taken daily for 20 to 22 days, followed by a seven-day pill-free interval during which withdrawal bleeding is expected to occur (IARC 1999, HSDB 2009).

Steroidal estrogens are used to relieve certain symptoms of breast cancer in some women and men with metastatic disease and are used in the treatment of prostate cancer (androgen-dependent carcinoma). Steroidal estrogens, often in combination with progestogens or androgens, are also used to treat amenorrhea, endometriosis, and postpartum breast engorgement. Some estrogens, such as conjugated estrogens and estrone, have been used in cosmetic products (IARC 1979b). Estrogens (such as estradiol-17β and ethinylestradiol) are also used in a variety of veterinary treatments. Steroidal estrogens are also used in biochemical research (HSDB 2009).

Production

In the United States, commercial production of some steroidal estrogens was first reported in the late 1930s through the 1960s (estradiol-17β in 1939, estrone in 1941, ethinylestradiol in 1945, and conjugated estrogens in 1968) (IARC 1979b). Steroidal estrogens are isolated from the urine of pregnant horses or are synthesized. The available data suggest that the metabolism of estrogens in horses is similar to that in humans (IARC 1999). The principal estrogen present in conjugated estrogens is sodium estrone sulfate (between 52.5% and 61.5%). The estrogenic potency of conjugated estrogens is expressed by the equivalent quantity of sodium estrone sulfate. Conjugated estrogens also contain sodium equilin sulfate (between 22.5% and 30.5%) (IARC 1999).

Ethinylestradiol, mestranol, estradiol, estradiol benzoate, and estradiol valerate are produced or formulated in the United States, but no production figures have been reported (IARC 1999). In the early 1970s, annual U.S. sales were estimated to be less than 50 kg (110 lb) for ethinylestradiol, 100 kg (220 lb) for mestranol, 100 kg (220 lb) for estradiol-17β, and 2,000 kg (4,400 lb) for estrone (IARC 1974). In 1975, U.S. production of 13 estrogenic and progestogenic substances, including conjugated estrogens, amounted to about 10,500 kg

(23,100 lb) (IARC 1979b). No recent data on production volumes were found. Numbers of U.S. suppliers of selected steroidal estrogens in 2010 were 18 for estradiol-17β, 15 for estrone, 14 for ethinylestradiol, 13 for mestranol, 1 for sodium estrone sulfate, 3 for piperazine estrone sulfate, and 1 for sodium equilin sulfate. (ChemSources 2010). U.S. imports of “estrogens of animal or vegetable origin” were 6,765 kg (14,914 lb) in 2000 and 5,689 kg (12,516 lb) in 2009. Other import categories included “estradiol cyclopentylpropionate (estradiol cypionate); estradiol benzoate,” with imports of 1,406 kg (3,100 lb) in 2000 and 653 kg (1,437 lb) in 2009, and “estrogens not derived from animal or vegetable materials,” with imports of 8,766 kg (19,325 lb) in 2000 and 1,002 kg (2,204 lb) in 2002. U.S. exports of “estrogens and progestins” were 128,152 kg (282,522 lb) in 2000 and 29,028 kg (63,861 lb) in 2009 (USITC 2010).

Exposure

Under normal conditions, the ovaries produce estrogens in response to pituitary hormones. Estradiol is the main naturally occurring estrogen. Estradiol is substantially more potent at the receptor level than its metabolites estrone and estriol. In a woman with a normal menstrual cycle, the ovary releases 70 to 500 µg of estradiol per day, depending on the phase of the cycle. This estradiol is converted mainly to estrone and also to small amounts of estriol. After menopause, most estrogen naturally occurring in a woman's body comes from peripheral tissues that produce estrone from androstenedione, a hormone released by the adrenal cortex. Estrone and its sulfate-conjugated form, estrone sulfate, are the most abundant circulating estrogens in postmenopausal women (IARC 1999). Estrone is found in the urine of pregnant women and mares, in bulls and stallions, in ovarian fluids of many animals, in human placentas, and in palm-kernel oil. Conjugated estrogens are naturally occurring substances found in the urine of pregnant mares (IARC 1979b). Over 360 plants have been identified that have estrogenic activity, and a few plants contain the principal estrogens found in mammals (estradiol and estrone) (Setchell 1985). Meat and milk also may contain estrogens (Collins and Musey 1985). Veterinary use of steroidal estrogens (to promote growth and treat illnesses) can increase estrogens in tissues of food-producing animals to above their normal levels.

Conjugated estrogens used in combined oral contraceptives are available as tablets, and those used for postmenopausal estrogen therapy are available in tablets, transdermal patches and gels, vaginal inserts and creams, subcutaneous implants, and injectable formulations. In 2009, over 84 million prescriptions were filled for brand-name and generic products containing estrogens (either conjugated or esterified) as an active ingredient (DrugTopics 2009a). The retail value of estrogen-containing products sold in that year exceeded \$2.6 billion (DrugTopics 2009b).

Oral contraceptive use in the United States began in 1960, but before then, estrogen preparations were used to treat menstrual disorders. Oral contraceptive use increased rapidly into the mid 1970s, but declined in the late 1970s because of increased awareness that oral contraceptives increased the risk of heart disease. The percentage of women born in the United States between 1945 and 1949 who have ever used oral contraceptives is 85%, compared with 60% of women born a decade earlier and less than 30% of women born before 1930. Pills with lower doses of estrogen were developed in the 1970s and 1980s, and those containing more than 50 µg of estrogen were slowly eliminated. The first combined oral contraceptive pills contained more than three times the amount of estrogen and progestogen used in current formulations. The standard dose is 30 to 35 µg of estrogen, with lower doses available (IARC 1999).

The use of postmenopausal estrogen therapy also became common in the United States in the 1960s. Between 1962 and 1967, the number of women using this therapy increased by 240%. By 1967, approximately 13% of the women in the United States 45 to 64 years old used this type of therapy. The number of prescriptions for estrogens, not counting those used for oral contraceptives, increased from 15 million in 1966 to over 25 million in 1976. Prescriptions had declined to 15 million by 1982 because of concerns about endometrial cancer but again increased rapidly to 40 million by 1992. Doses used in postmenopausal estrogen therapy vary with the indication and the method of administration. Typical daily doses for treatment of menopausal symptoms are 0.625 to 1.25 mg of conjugated equine estrogens or 0.5 to 4.0 mg of estradiol. Minimal daily doses used to prevent osteoporosis are 0.625 mg of conjugated equine estrogens (pills), 2 mg of estradiol (pills), or 0.05 mg of estradiol (skin patch). Transdermal implants may contain 50 to 100 mg of estradiol and last for six to nine months (IARC 1999).

Estrone has also been used in hormonal skin preparations for cosmetic use at concentrations of less than 0.1%. Unspecified estrogen and estrogenic hormones, which are believed to consist primarily of estrone, have been used in hormonal skin preparations (less than 0.1% to 5%), moisturizing lotions (1% to 5%), wrinkle-smoothing creams, hair conditioners, hair straighteners, shampoos, and grooming-aids tonics (less than 0.1%) (IARC 1979b).

Potential exposure to steroidal estrogens in the workplace may occur through inhalation or dermal contact during production, processing, or packaging. In a facility producing oral contraceptives, mestranol was found in various sectors of the work environment at air concentrations ranging from 0.06 to 8.61 µg/m³ and on samples wiped from surfaces at levels of 0.003 to 2.05 µg/cm² (IARC 1979b). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that in 1970, 2,770 workers potentially were exposed to specific steroidal estrogens (ethinylestradiol, estrone, estradiol-17β) (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,083 workers potentially were exposed to estradiol-17β and 4,444 to estrone (NIOSH 1990).

Regulations

Consumer Products Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging; however, conjugated estrogen tablets dispensed in mnemonic packages containing no more than 32 mg do not require child-resistant packaging.

Food and Drug Administration (FDA)

Estrogens are prescription drugs subject to labeling and other requirements. Estradiol residue limits in animal tissues for human consumption are prescribed in 21 CFR 556.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Ethylene Oxide

CAS No. 75-21-8

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Ethylene oxide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological studies and studies on mechanisms of carcinogenesis. Ethylene oxide was first listed in the *Fourth Annual Report on Carcinogens* in 1985 as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals. The listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000.

An increased risk of cancer has been demonstrated in epidemiological studies of workers using ethylene oxide as a sterilant for medical devices and spices and in chemical synthesis and production. Evidence for a common mechanism of carcinogenesis in humans and experimental animals comes from studies that have found similar genetic damage in cells of animals and workers exposed to ethylene oxide. The DNA-damaging activity of ethylene oxide explains

its effectiveness as a sterilant, and this same property accounts for its carcinogenic risk to humans.

Cancer Studies in Humans

Several epidemiological studies reported an association between exposure to ethylene oxide and increased risk of leukemia and stomach cancer; however, other studies found no significantly increased risks of cancer (Steenland *et al.* 1991, Teta *et al.* 1993, IARC 1994). In most studies, information on the extent of exposure to ethylene oxide was limited. The types of cancer most frequently reported to be associated with occupational exposure to ethylene oxide were lymphoma and leukemia (IARC 1994). The likelihood of confounding occupational exposures to other chemicals generally is lower for sterilization workers than for chemical synthesis and production workers.

A meta-analysis of 10 distinct cohort studies of workers exposed to ethylene oxide found no association between exposure and risk of pancreatic or brain cancer; however, this analysis suggested associations with non-Hodgkin's lymphoma and stomach cancer (Shore *et al.* 1993). The largest study of U.S. workers exposed to ethylene oxide at plants producing sterilized medical supplies or spices found no excess mortality from any cause of death; however, males workers had excess mortality from all cancer of the hematopoietic system combined (especially lymphosarcoma, reticulosarcoma, and non-Hodgkin's lymphoma) (Steenland *et al.* 1991). Risk of mortality from all lymphatic and hematopoietic cancer increased with increasing cumulative exposure to ethylene oxide, and this trend was strengthened when the analysis was restricted to cancer of lymphoid-cell origin (lymphocytic leukemia and non-Hodgkin's lymphoma combined). Increasing cumulative exposure to ethylene oxide was associated with increased risk of leukemia, but this trend was not statistically significant (Stayner *et al.* 1993). Other studies reported elevated risk of leukemia in workers who had been exposed to ethylene oxide for more than 10 years (Teta *et al.* 1993) and elevated incidence of breast cancer in a cohort of workers who used ethylene oxide as a sterilant (Norman *et al.* 1995).

Studies on Mechanisms of Carcinogenesis

Ethylene oxide is a direct-acting alkylating agent that forms adducts with biological macromolecules, including hemoglobin and DNA. Ethylene oxide caused dose-related increases in the frequency of hemoglobin adducts in exposed humans and rodents. Measurements of hemoglobin adducts (hydroxyethyl histidine and hydroxyethyl valine) have been used to monitor worker exposure to ethylene oxide (IARC 1994). The major DNA adduct of ethylene oxide is *N*7-(2-hydroxyethyl)guanine. Dose-related increases in this adduct, as well as smaller amounts of *O*⁶-(2-hydroxyethyl)guanine and *N*3-(2-hydroxyethyl)adenine, were observed in rodents exposed to ethylene oxide. It has been suggested that background levels of hemoglobin and DNA adducts of ethylene oxide in humans and experimental animals arise from endogenous production of ethylene by intestinal flora or metabolism of unsaturated dietary lipids (Tornqvist 1996).

Ethylene oxide caused genetic damage in all species studied, including prokaryotic, lower eukaryotic, and *in vitro* and *in vivo* mammalian systems. Ethylene oxide caused gene mutations and heritable translocations in germ cells of rodents exposed *in vivo*. In occupationally exposed workers, ethylene oxide caused dose-related increases in the frequencies of chromosomal aberrations, sister chromatid exchange, *hprt* mutations in peripheral lymphocytes, micronucleus formation in erythrocytes, and DNA single-strand breaks in peripheral mononuclear blood cells (Fuchs *et al.* 1994, IARC 1994, Oesch *et al.* 1995, Schulte *et al.* 1995, Major *et al.* 1996). Similar genotoxic effects were observed in rodents exposed to ethylene oxide (IARC 1994). For

direct-acting mutagenic chemicals, increases in chromosome aberration frequency appear to be a good predictor of increased human cancer risk. Thus, all measurable genotoxic end points that are considered to be indicators of chemical carcinogenesis have been observed in both humans and experimental animals exposed to ethylene oxide.

Cancer Studies in Experimental Animals

Inhalation exposure to ethylene oxide caused tumors at several different tissue sites in rodents, including the hematopoietic system in mice and rats; the lung, Harderian gland, mammary gland, and uterus in mice; and the brain and mesothelium in rats (NTP 1987, IARC 1994).

Properties

Ethylene oxide is the simplest epoxy compound, which at room temperature is a colorless gas with a sweet odor. It is miscible with water, alcohol, and most organic solvents and soluble in acetone. Ethylene oxide is flammable and explosive, and incomplete combustion releases carbon monoxide (IARC 1994). Physical and chemical properties of ethylene oxide are listed in the following table.

Property	Information
Molecular weight	44.1 ^a
Specific gravity	0.882 at 10°C/10°C ^a
Melting point	-111°C ^a
Boiling point	10.7°C at 760 mm Hg ^a
Log K_{ow}	-0.3 ^a
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	1314 mm Hg at 25°C ^a
Vapor density relative to air	1.49 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Ethylene oxide is available commercially in the United States as a high-purity chemical containing no more than 0.03% water, 0.003% aldehydes as acetaldehyde, or 0.002% acidity as acetic acid. It has been sold as a mixture with either carbon dioxide or fluorocarbon 12 to reduce its fire hazard (HSDB 2009).

Use

The major use of ethylene oxide in the United States (accounting for over 99% of production) is as an intermediate in the production of several industrial chemicals (ATSDR 1990, IARC 1994). The remainder is used in the gaseous form, either alone or combined with nitrogen, carbon dioxide, or dichlorofluoromethane as a sterilizing agent, disinfectant, fumigant, or insecticide. The largest use (about 60%) is to produce ethylene glycol (antifreeze). Other chemicals produced from ethylene oxide include non-ionic surfactants (used in industrial applications, detergents, and dishwashing formulations), glycol ethers, ethanolamines (used in soaps, detergents, and textile chemicals), diethylene glycol, triethylene glycol, polyethylene glycol, and urethane polyols. Although a relatively small percentage of ethylene oxide is used as a fumigant or sterilizing agent, these uses involve a variety of facilities, products, and materials, including hospital equipment, medical and dental clinics, research laboratories, foods, furs, clothing, furniture, books, paper, leather, cosmetics, drugs, railroad cars, beehives, and tobacco. Facilities that manufacture sterile disposable medical supplies and medical facilities, including hospitals, medical and dental clinics, and private medical and dental surgeries, account for about 95% of the ethylene oxide used as a fumigant or sterilant. In hospitals, ethylene oxide is used as a gaseous sterilant for heat-sensitive medical items, surgical instruments, and other objects and fluids coming in contact with biological tissues. Before 1966, ethylene oxide was used as an intermediate in the production of acrylonitrile.

Production

Ethylene oxide was first produced in the United States in 1921. Until 1937, it was produced by the chlorohydrin process, in which ethylene was treated with hypochlorous acid to produce ethylene chlorohydrin, and calcium hydroxide or sodium hydroxide was used to convert ethylene chlorohydrin to ethylene oxide. Essentially all U.S. production of ethylene oxide now uses the direct vapor phase oxidation process, by which ethylene is oxidized with air or oxygen in the presence of a silver catalyst to produce ethylene oxide. In addition, ethylene oxide is produced naturally as a metabolite of ethylene and has been identified in automobile and diesel exhaust and in tobacco smoke (IARC 1994).

Ethylene oxide is a major industrial chemical and is consistently ranked among the 25 highest-production-volume chemicals produced in the United States. U.S. production was 4 billion pounds in 1973, 6 billion pounds in 1979, 5 billion pounds in 1987 (ATSDR 1990), 2.6 million metric tons (5.8 billion pounds) in 1992, and 3.4 million metric tons (7.6 billion pounds) in 2002. Peak production of slightly over 4 million metric tons (8.9 billion pounds) was reported in 1999 (CEN 2003). In 2009, 12 U.S. manufacturers (SRI 2009) and 10 U.S. suppliers of ethylene oxide were identified (ChemSources 2009). In 2008, U.S. imports of ethylene oxide were 3 million pounds, and U.S. exports were 1.9 million pounds (USITC 2009).

Exposure

The primary routes of potential human exposure to ethylene oxide are inhalation and ingestion, which may occur through occupational, consumer, or environmental exposure. Exposure by dermal contact is expected to be low under most circumstances. Little information is available on dermal exposure; however, industrial workers whose skin was accidentally exposed to aqueous solutions of ethylene oxide have experienced nausea and vomiting (WHO 1985).

The general population may be exposed to ethylene oxide through use of products that have been sterilized with the compound, such as medical products, food, clothing, cosmetics, beekeeping equipment, and other products (NIOSH 1981, ATSDR 1990). People who live near industrial facilities that produce or use ethylene oxide may be exposed from uncontrolled industrial emissions (see below). Ethylene oxide has been detected in tobacco smoke, automobile exhaust, and some foods and spices; however, few data are available that can be used to estimate exposure levels. Fumigated products may initially contain high levels of ethylene oxide, but it degrades or disperses within a few days. One study found that ethylene oxide levels in most experimentally fumigated commodities were less than 1 ppm after 14 days under normal storage conditions. Concentrations of ethylene oxide in fumigated grains, spices, dates, and peas ranged from 0 to 3.5 ppm after 24 hours. Another study reported concentrations in spices ranging from 53 to 116 ppm after 2 days and about 25 ppm after 26 days (ATSDR 1990).

Industrial releases of ethylene oxide to the environment occur during its storage and handling in industrial facilities, including uncontrolled fugitive emissions or venting with other gases. From 1978 to 1980, 1.3 million to 3 million pounds of ethylene oxide was released to air during ethylene oxide production, and another 143,000 lb was released during storage (ATSDR 1990). Other sources of ethylene oxide emissions to air include its production during combustion of hydrocarbon fuel (including in automobile exhaust), its release from fumigated materials, and losses during disinfection of hospital equipment. Annual releases from fumigated materials were estimated at about 10 million pounds from 1978 to 1980. Estimates of annual releases from commercial sterilization facilities ranged from 1,146 to 44,092 lb per unit (EPA 1993).

Industrial releases of ethylene oxide to water are relatively minor, compared with fugitive air emissions. Although an estimated 800,000 lb of ethylene oxide was discharged annually to wastewater treatment systems in the late 1970s and early 1980s, it was not detected in the treated wastewaters discharged to waterways (ATSDR 1990). Conventional wastewater treatment, including biological treatment, is very effective in removing ethylene oxide from wastewater. No specific solid wastes are produced by the manufacture of ethylene oxide (WHO 1985). Ethylene oxide degrades in water and air with half-lives ranging from a few hours to 15 to 20 days, depending on the environmental conditions. Therefore, even though relatively large amounts of ethylene oxide are released from industrial facilities, it is not a commonly reported environmental contaminant (ATSDR 1990).

Releases of ethylene oxide to the environment have decreased markedly since 1988, when about 5 million pounds was released, according to the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009). Since 1988, releases to surface water have accounted for 1% or less of total environmental releases, while releases to air have accounted for 93% or more. The remainder of releases have been to underground injection wells, land, and off-site treatment. In 2007, 115 industrial facilities reported environmental releases of ethylene oxide to the environment totalling over 311,000 lb, of which about 93% was released to air, 4% to underground injection, 1% to surface water, and the remainder to off-site treatment and disposal. Occupational exposure to ethylene oxide may occur among workers involved in ethylene oxide production, in the manufacture of its end products, or in its use in hospital and industrial sterilization (ATSDR 1990, IARC 1994). Industrial and health-care workers may be exposed to ethylene oxide during sterilization of a variety of products, such as medical equipment and products (e.g., surgical products or single-use medical devices), disposable health-care products, pharmaceutical and veterinary products, spices, and animal feed (IARC 1994).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that about 141,000 U.S. workers in 67 nonagricultural industries potentially were exposed to ethylene oxide (NIOSH 1976). In 1977, the National Institute for Occupational Safety and Health estimated that 75,000 health-care workers employed in sterilization areas potentially were exposed to ethylene oxide, and that an additional 25,000 hospital workers in other areas may have been incidentally exposed (NIOSH 1981). The Occupational Safety and Health Administration estimated that in 1983, 80,000 U.S. health-care workers were directly exposed to ethylene oxide, and 144,000 workers in the medical device and related industries were incidentally exposed (NCI 1985). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 270,767 workers, including 120,086 were women, potentially were exposed to ethylene oxide (NIOSH 1990).

Because ethylene oxide is highly explosive and reactive, the equipment used for its processing generally consists of tightly closed and highly automated systems, which decreases the risk of occupational exposure (NCI 1985). A 1979 survey of U.S. plants producing and using ethylene oxide reported daily average concentrations of 0.5 to 7.3 mg/m³ (0.3 to 4 ppm), with a maximum worst-case peak concentration of 17,500 mg/m³ (9,600 ppm). A review of exposure data collected in 1987 from 11 U.S. ethylene oxide production facilities reported that the highest mean 8-hour time-weighted-average (TWA) concentration was 2.9 mg/m³ (1.6 ppm), with a range of 0.36 to 6.8 mg/m³ (0.20 to 3.8 ppm); mean short-term exposure levels for maintenance workers were as high as 19.6 mg/m³ (10.9 ppm) (IARC 1994).

In industrial and health-care use of ethylene oxide sterilization, workers may be exposed during changing of pressurized ethylene oxide

gas cylinders; from leaking valves, fittings, piping, and sterilizer door gaskets; from opening of the sterilizer door at the end of a cycle; from improper ventilation at the sterilizer door; from an improperly ventilated or unventilated air gap between the discharge line and the sewer drain; during removal of items from the sterilizer and transfer of the sterilized load to an aerator; from improper ventilation of aerators and aeration areas; from incomplete aeration of items; from inadequate general room ventilation; and from passing near sterilizers and aerators during operation. Health-care technicians can be exposed to short, concentrated bursts of the gas when the door of a sterilizing machine is opened (Sun 1986). A large survey of 21 companies involved in ethylene oxide sterilization (primarily of medical supplies and spices) conducted from 1976 to 1985 estimated that sterilizer operators were exposed to 8-hour TWA concentrations of 16 ppm before 1978 and 4 to 5 ppm after 1978 (IARC 1994).

A study conducted in Massachusetts hospitals from 1990 to 1992 found that 23% of hospitals exceeded the OSHA action level of 0.5 ppm at least once, 24% exceeded the short-term exposure limit of 5 ppm, and 33% reported accidental exposures to ethylene oxide in the absence of personal monitoring (LaMontagne and Kelsey 1997). However, other studies have shown that industrial hygiene measures can effectively control ethylene oxide exposure in hospitals and other places where it is used as a sterilant. An evaluation of nine sterilizer control systems in eight hospitals found that control technologies could reduce average ethylene oxide concentrations to less than 0.1 ppm for a full shift and maximum concentrations to within a ceiling limit of 5 ppm (Mortimer and Kercher 1989). Another evaluation found that standard industrial hygiene practices could result in nearly zero exposure to ethylene oxide in hospitals; peak levels were reduced from 500 ppm to less than 2.8 ppm through the use of engineering and administrative controls (Elias *et al.* 1993).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of ethylene oxide on ships and barges.

Department of Transportation (DOT)

Ethylene oxide mixtures are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of ethylene oxide is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Threshold planning quantity (TPQ) = 1,000 lb.

Reportable quantity (RQ) = 10 lb.

Federal Insecticide, Fungicide, and Rodenticide Act

The tolerance for residues of ethylene oxide when used as a fumigant on coconut, walnuts, and spices = 50 ppm.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of ethylene oxide = U115.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Regulations for ethylene oxide and polymers and copolymers of ethylene oxide used as direct or indirect food additives are prescribed under 21 CFR 172, 173, 175, 176, and 178.

Specific labeling is required for its use as an antimicrobial agent and insecticide.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm. Acceptable peak exposure = 5 ppm (15-min excursion). Comprehensive standards for occupational exposure to ethylene oxide have been developed.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (time-weighted-average workday) = < 0.1 ppm (0.18 mg/m³). Ceiling recommended exposure limit = 5 ppm (9 mg/m³) (10 min/day). Immediately dangerous to life and health (IDLH) limit = 800 ppm. Listed as a potential occupational carcinogen.

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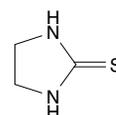
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Ethylene Thiourea**CAS No. 96-45-7**

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

**Carcinogenicity**

Ethylene thiourea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to ethylene thiourea caused tumors in two rodent species and at two different tissue sites. Administration of ethylene thiourea by stomach tube for three weeks followed by dietary administration for an additional 80 weeks caused liver cancer (hepatocellular carcinoma) in mice of both sexes, and dietary administration of ethylene thiourea caused thyroid-gland cancer (follicular-cell carcinoma) in rats of both sexes (IARC 1974).

Since ethylene thiourea was listed in the *Fourth Annual Report on Carcinogens*, additional studies in rodents have been identified. Studies conducted by the National Toxicology Program compared the effects of adult exposure, perinatal exposure, and combined perinatal and adult exposure to ethylene thiourea in mice and rats (NTP 1992, IARC 2001). Dietary exposure of adult animals to ethylene thiourea caused thyroid-gland cancer (follicular-cell carcinoma) in mice and rats of both sexes, liver cancer (hepatocellular carcinoma) in mice of both sexes, and benign pituitary-gland tumors (adenoma of the pars distalis) in mice of both sexes. Perinatal exposure only (via dietary exposure of pregnant and lactating animals) did not increase the incidence of thyroid-gland tumors. Combined perinatal and adult exposure caused tumors at the same tissue sites as observed for adult-only exposure (except that the incidence of benign pituitary-gland tumors was increased only in female mice). However, combined exposure increased the proliferative effects of ethylene thiourea on thyroid follicular cells in both sexes of both species and may also have been responsible for increased incidences of mononuclear-cell leukemia and Zymbal-gland tumors in rats of both sexes.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to ethylene thiourea. One study of 1,929 rubber-manufacturing workers in the United Kingdom who were potentially exposed to ethylene thiourea reported no cases of thyroid cancer (based on cancer registry records) (IARC 1987). However, the statistical power to detect an effect was inadequate, and no data were provided on exposure, age, sex, length of employment, or duration of follow-up.

Properties

Ethylene thiourea is a heterocyclic compound that exists at room temperature as white to pale-green needle-like crystals with a faint amine odor. It is soluble in water, ethanol, naphtha, and acetic acid, slightly soluble in methanol, ethylene glycol, and pyridine, and insoluble in acetone, chloroform, ligroin, ethyl ether, and benzene (HSDB 2009). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of ethylene thiourea are listed in the following table.

Property	Information
Molecular weight	102.2 ^a
Density	1.417 g/cm ^{3b}
Melting point	199°C to 204°C ^a
Boiling point	347°C ^c
Log <i>K</i> _{ow}	-0.66 ^a
Water solubility	20 g/L at 30°C ^a
Vapor pressure	2.02 × 10 ⁻⁶ mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Ethylene thiourea is used primarily as an accelerator for vulcanizing polychloroprene (neoprene) and polyacrylate rubbers (IARC 1974, 2001, HSDB 2009). Neoprene rubbers are used almost exclusively in industrial applications, including industrial and mechanical goods, automotive products, wire and cable production, construction, and adhesives (IARC 1974). Polyacrylate rubbers are used in products such as seals, o-rings, and gaskets for automotive and aircraft applications. Ethylene thiourea is also used in electroplating baths, as an intermediate in antioxidant production, and in dyes, pharmaceuticals, and synthetic resins.

Production

Commercial production of ethylene thiourea was first reported in the United States in 1951 (IARC 1974). In 1977, U.S. production of ethylene thiourea was about 100,000 lb, and U.S. imports totaled about 10,000 lb (HSDB 2009). By 1980, production had fallen to about 1,000 lb. No commercial producers or production volumes were found for ethylene thiourea in 2009 (SRI 2009); however, 24 suppliers were identified worldwide, including 12 U.S. suppliers (ChemSources 2009). No recent U.S. import or export data specifically for ethylene thiourea were found. However, reports filed in 1986, 1994, 1998, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of ethylene thiourea totaled 10,000 to 500,000 lb (EPA 2004). No inventory update reports were filed in 1990.

Exposure

The routes of potential human exposure to ethylene thiourea are inhalation, ingestion, and dermal contact (HSDB 2009). The primary source of these exposures is the use of ethylenedisithiocarbamate (EBDC) fungicides (e.g., amobam, mancozeb, maneb, metiram,

nabam, and zineb), of which ethylene thiourea is an environmental degradation product, metabolite, and impurity (IARC 2001). Ethylene thiourea content in EBDC fungicides depends on the pesticide storage conditions and increases with increasing temperature, moisture, and length of storage (Camoni *et al.* 1988). EPA has grouped these pesticides based on the common mechanism of formation of ethylene thiourea (EPA 2005b), and EPA's reregistration eligibility decisions for mancozeb, maneb, and metiram are based on ethylene thiourea as a metabolite, environmental degradate, and cooking by-product of these fungicides (EPA 2005c,d,e). About 7.5 million pounds of mancozeb, 2.5 million pounds of maneb, and 0.9 million pounds of metiram are used annually, including use on food crops, ornamental plants, and sod.

Ethylene thiourea has been measured in food products, where it is believed to be a metabolite of EBDC fungicides (Houeto *et al.* 1995). Ethylene thiourea was found in beer at concentrations of 0.026 to 0.07 ppm and in wine at 0.037 ppm. The U.S. Food and Drug Administration's Total Diet Study found ethylene thiourea in 27 different products, at concentrations ranging from 0.003 ppm (the limit of quantitation) to 0.276 ppm; the highest concentrations were found in spinach and collards (FDA 2006). In kale and lettuce treated with maneb at a rate of 1.09 kg of active ingredient per acre, ethylene thiourea residues were initially 0.6 mg/kg, decreasing to undetectable levels within seven days after application (IARC 1974). Ethylene thiourea has been detected on apples sold for human consumption at concentrations of 0.018 to 0.044 mg/kg. It can also be formed when foods treated with EBDC fungicides are cooked (NIOSH 1978). A high concentration of 71 mg/kg was measured in spinach sprayed four times in the field with mancozeb and canned without washing (Lentza-Rizos 1990). In a study conducted in Germany, ethylene thiourea was measured in market samples of pears (0.205 ppm) and lamb's lettuce (0.367 ppm) (Dubey *et al.* 1997). Ethylene thiourea concentrations were much lower in the fruits than in the leaves of eggplants treated directly with ethylene thiourea (Kumar and Agarwal 1993). Ethylene thiourea has also been identified in cigarette smoke (IARC 2001); burning cigarettes were reported to produce 16 µg of ethylene thiourea per gram of tobacco (Houeto *et al.* 1995).

Since 2005, only commercial uses of EBDC fungicides have been permitted (EPA 2005a). The U.S. EPA estimated exposure of the general population to ethylene thiourea from past use in residential and other non-occupational scenarios, such as use of mancozeb on home gardens, golf courses, and lawns, to be below the level of concern (EPA 2005b).

Although the curing of rubber converts ethylene thiourea to other compounds, trace amounts of ethylene thiourea are present in cured rubber products (IARC 1974). Testing of a specific neoprene stock indicated that 0.01 mg of unchanged ethylene thiourea per square inch of surface could be extracted by water at 57°C over a period of seven days. Consumer products containing neoprene include shoes and closures for containers (e.g., aerosol dispensers).

According to EPA's Toxics Release Inventory, the largest total releases of ethylene thiourea were reported in 2006, when more than 29,000 lb was released, mostly to off-site non-hazardous-waste landfills. In 2009, 1,945 lb of ethylene thiourea was released to the environment from one facility, nearly all to an off-site non-hazardous-waste landfill (TRI 2009). Ethylene thiourea released to air will exist in the vapor phase and will be degraded by photochemically produced hydroxyl radicals, with a half-life of 2 hours (HSDB 2009). When released to water, it will remain in the water column and will not be likely to adsorb to sediments or to volatilize. It is unlikely to bioaccumulate in aquatic organisms. In soil, it will be highly mobile but will be rapidly biodegraded, especially near the soil surface.

Because ethylene thiourea is very soluble and moderately mobile in the environment, it potentially could be found in drinking water from both surface water and groundwater sources. It was measured at 0.21 ppb in the raw water from one public drinking-water well. However, it was not detected in any of 84 sampled finished drinking water sources, and a targeted study did not detect ethylene thiourea in surface water (detection limit = 0.1 ppb (EPA 2005b,c,d). Ethylene thiourea was detected in 1 of 183 tested U.S. groundwater wells at a concentration of 0.7 mg/L, and it has been estimated that 0.1% of rural wells in the United States are contaminated with ethylene thiourea.

Exposed individuals have been shown to have measurable concentrations of ethylene thiourea in their urine. It has been measured in the urine of the general population in Italy at concentrations as high as 61.4 µg/g of creatinine (Aprea *et al.* 1996, 1997, Colosio *et al.* 2006). The higher concentrations were attributed to wine consumption greater than 500 mL per day by rural male individuals.

Potential occupational exposure to ethylene thiourea is greatest for workers involved in metal fabrication, manufacture of machinery, manufacture of rubber and rubber products, and manufacture, formulation, and application of EBDC pesticides (IARC 2001). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 3,500 workers potentially were exposed to ethylene thiourea during the manufacture of rubber products (NIOSH 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 10,749 workers, including 1,804 women, but not including agricultural workers, potentially were exposed to ethylene thiourea (NIOSH 1990). Samples taken in an ethylene thiourea manufacturing facility in 1976 found concentrations in personal air samples of up to 330 µg/m³ and background levels in the range of 10 to 240 µg/m³ (Smith 1984). In a second ethylene thiourea manufacturing facility, sampled in 1980, concentrations in personal samplers ranged from 120 to 160 µg/m³. Among workers in Italy producing commercial formulations of mancozeb, the urinary concentration of ethylene thiourea was highest in workers formulating pesticide in powder form (median = 55.4 µg/g of creatinine), reflecting the higher concentrations found in the air (1.9 µg/m³), in the hand-wash residue (36.9 to 194.3 µg), and in pads attached to the workers' necks (15 to 96 ng/cm²) in the area of the plant where the pesticide powder was formulated (Aprea *et al.* 1998).

Among agricultural workers in Italy who regularly handled EBDC pesticides, pre-exposure urinary concentrations ranged from 0.5 to 2.1 µg/L and post-exposure concentrations from 1.9 to 8.2 µg/L (Sotani *et al.* 2003). In another study in Italy, workers had pre-exposure concentrations of less than 1.6 µg/g of creatinine and a post-exposure median concentration of 8.5 µg/g, with a maximum of 40.1 µg/g (Fustinoni *et al.* 2005). A third study in Italy confirmed these findings (Corsini *et al.* 2005). Ethylene thiourea was measured at a mean concentration of 58 ppb in the urine of 49 agricultural workers in Mexico who applied EBDCs in backpack sprayers to tomatoes and at 12 ppb in 14 owners of the farms, but was not detected in the urine of 31 unexposed control subjects. Ethylene thiourea was measured in the blood and urine of banana plantation workers in the Philippines; in directly exposed workers, mean concentrations were 4.4 ppb in blood and 378.3 ppb in urine, compared with 0.3 ppb in the blood and 26.3 ppb in the urine of control subjects (Panganiban *et al.* 2004). Ethylene thiourea was also measured in the breathing zone of workers exposed to EBDCs in potato fields and pine nurseries; concentrations of up to 1.81 µg/m³ were measured in the area where the pesticide was weighed and mixed (Kurttio and Savolainen 1990). The mean level of ethylene thiourea in 24-hour urine samples ranged from 498 ng for the pine-nursery weeder to 3,746 ng for the potato-field workers (Savolainen *et al.* 1989, Kurttio and Savolainen 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of ethylene thiourea = U116.

Listed as a hazardous constituent of waste.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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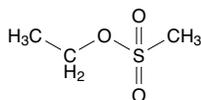
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select Ethylene Thiourea. Last accessed: 5/19/09.

Ethyl Methanesulfonate

CAS No. 62-50-0

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)



Carcinogenicity

Ethyl methanesulfonate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Ethyl methanesulfonate caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Ethyl methanesulfonate caused benign or malignant lung tumors (adenoma or carcinoma) when administered by subcutaneous injection to newborn mice and by intraperitoneal injection to adult mice and rats. When administered by intraperitoneal injection, it also caused benign or malignant kidney tumors in male mice and in rats (renal carcinoma in female rats and malignant epithelial and mesenchymal tumors in rats of both sexes). In these studies, a single injection was sufficient to cause lung tumors in newborn and adult mice and kidney tumors in rats (IARC 1974). Oral exposure to ethyl methanesulfonate caused kidney tumors in female rats and cancer of the

mammary gland (adenocarcinoma) in rats of both sexes (Ueo *et al.* 1981). An additive effect on the incidence of kidney cancer was seen in rats receiving a single intraperitoneal injection of dimethylnitrosamine (*N*-nitrosodimethylamine) followed by a single intraperitoneal injection of ethyl methanesulfonate (IARC 1974).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to ethyl methanesulfonate.

Properties

Ethyl methanesulfonate is the ethyl ester of methanesulfonic acid and exists as a colorless liquid at room temperature (IARC 1974). It is soluble in water and stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of ethyl methanesulfonate are listed in the following table.

Property	Information
Molecular weight	124.2 ^a
Specific gravity	1.15 at 22°C/4°C ^a
Melting point	< -25°C ^b
Boiling point	213°C to 214°C at 761 mm Hg ^a
Log <i>K</i> _{ow}	0.09 ^a
Water solubility	135 g/L at 25°C ^b
Vapor pressure	0.328 mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Ethyl methanesulfonate is used experimentally as a mutagen and as a biochemical research reagent (Akron 2009, HSDB 2009).

Production

In 2009, no commercial manufacturers of ethyl methanesulfonate were identified worldwide (SRI 2009), but it was available from 24 suppliers, including 13 U.S. suppliers (ChemSources 2009). No data were found on U.S. imports or exports of ethyl methanesulfonate in 2009.

Exposure

Exposure to ethyl methanesulfonate is expected to be limited to laboratory researchers. It has been identified as a trace contaminant in pharmaceutical products (Li 2004). When released to air, ethyl methanesulfonate will exist almost entirely in the vapor phase and may react with photochemically produced hydroxyl radicals, with an estimated half-life of 30 days. It hydrolyzes relatively rapidly in water or moist soil, with an estimated half-life of 96 hours at 20°C, and is expected to volatilize from dry soil. It is not expected to bind to soil or sediment. It is therefore not expected to persist in the environment or to bioconcentrate in aquatic organisms. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 971 workers, including 448 women, potentially were exposed to ethyl methanesulfonate (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of ethyl methanesulfonate = U119.

Listed as a hazardous constituent of waste.

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Formaldehyde

CAS No. 50-00-0

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Formaldehyde is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis. Formaldehyde was first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals. Since that time, additional cancer studies in humans have been published, and the listing status was changed to *known to be a human carcinogen* in the *Twelfth Report on Carcinogens* (2011).

Cancer Studies in Humans

Epidemiological studies have demonstrated a causal relationship between exposure to formaldehyde and cancer in humans. Causality is indicated by consistent findings of increased risks of nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia among individuals with higher measures of exposure to formaldehyde (exposure level or duration), which cannot be explained by chance, bias, or confounding. The evidence for nasopharyngeal cancer is somewhat stronger than that for myeloid leukemia.

Numerous epidemiological studies have evaluated the relationship between exposure to formaldehyde and cancer risk, including (1) cohort and nested case-control studies of industrial workers, (2) cohort and nested case-control studies of professional groups such as pathologists, funeral directors, or embalmers, and (3) population-based cohort and case-control studies. The most informative occupation-based studies are the National Cancer Institute (NCI) cohort of over 25,000 men and women who worked at companies that used or produced formaldehyde (Hauptmann *et al.* 2003, 2004, Beane Freeman *et al.* 2009) and the NCI nested case-control study of lymphohematopoietic cancer in embalmers (Hauptmann *et al.* 2009), because these

are the only studies that evaluated quantitative exposure-response relationships. Occupational exposure to formaldehyde has also been evaluated in two other large cohort studies: (1) a National Institute for Occupational Safety and Health (NIOSH) cohort study of over 11,000 male and female garment workers, which evaluated risks of cancer at a few selected tissue sites by time since first exposure (latency), exposure duration, and year of first exposure (Pinkerton *et al.* 2004), and (2) a British cohort study of over 14,000 male chemical workers, which evaluated cancer risks by classification of workers as “ever exposed” or “highly exposed” (Coggon *et al.* 2003). In addition, occupational exposure has been evaluated in numerous smaller cohort studies and the studies of professional groups, reported cancer mortality. For types of cancer with higher survival rates, such as lymphohematopoietic cancer, studies reporting mortality are less informative than studies reporting incidence, because mortality studies will miss cases of cancer that do not result in death.

For evaluating rare types of cancer, such as nasopharyngeal and sinonasal cancer, the collective body of population- and occupation-based case-control studies is more informative than the cohort studies. Particularly useful are the pooled analyses of 12 case-control studies of sinonasal cancer by Luce *et al.* (2002) and the population-based case-control study by Vaughan *et al.* (2000) evaluating different histological subtypes of nasopharyngeal cancer. In general, meta-analyses and smaller occupational cohort studies have limited utility for cancer assessment, because they only reported risks for workers “ever exposed” and could not evaluate exposure-response relationships. However, the meta-analysis for lymphohematopoietic cancers by Zhang *et al.* (2009) is more informative because it used data for individuals with the highest exposure to formaldehyde to calculate the summary relative risks.

Nasopharyngeal Cancer

Nasopharyngeal cancer is a rare cancer, with an annual incidence of less than 1 per 100,000 in most parts of the world. Therefore, case-control studies are most useful for evaluation of nasopharyngeal cancer risk. Histological subtypes of nasopharyngeal cancer include differentiated keratinizing squamous-cell carcinoma, differentiated non-keratinizing carcinoma, and undifferentiated non-keratinizing carcinoma. In southern China and some parts of Southeast Asia and Northern Africa, nasopharyngeal cancer is endemic, with a higher proportion of non-keratinizing and undifferentiated subtypes than in low-risk areas (Vaughan *et al.* 1996, Bray *et al.* 2008). Differentiated keratinizing squamous-cell carcinoma has been associated with chemical exposures, such as alcohol consumption and tobacco smoking, whereas non-keratinizing subtypes are more strongly associated with Epstein-Barr virus and familial history (which can be related to genetic susceptibility and/or common environmental factors). Studies on nasopharyngeal cancer and formaldehyde exposure have been conducted in the United States, Europe, and Asia.

Evidence that formaldehyde causes nasopharyngeal cancer comes from (1) consistent findings of increased risk among individuals with the highest formaldehyde exposure in numerous case-control studies (Vaughan *et al.* 1986, 2000, Roush *et al.* 1987, West *et al.* 1993, Hildesheim *et al.* 2001), (2) excess cancer mortality associated with formaldehyde exposure in the NCI cohort of industrial workers (Hauptmann *et al.* 2004), and (3) findings of positive exposure-response relationships in a large multi-center case-control study (Vaughan *et al.* 2000) and in the NCI cohort (Hauptmann *et al.* 2004).

The multi-center case-control study by Vaughan *et al.* (2000) is especially informative, because it had the largest number of cancer cases in formaldehyde-exposed individuals, and the analysis was strat-

ified by histological subtype and used several different measures of exposure to evaluate risk. In this study, formaldehyde exposure was associated with differentiated squamous-cell carcinoma and unspecified subtypes of nasopharyngeal cancer, but not with non-keratinizing and undifferentiated subtypes. The risk of nasopharyngeal cancer (differentiated squamous-cell carcinoma and unspecified subtypes) increased significantly with increasing cumulative exposure ($P_{\text{trend}} = 0.033$), duration of exposure ($P_{\text{trend}} = 0.014$), and probability of exposure (possible, probable, or definite). The odds ratio (OR) was 1.6 (95% confidence interval [CI] = 1.0 to 2.8, 61 exposed cases) for possible, probable, or definite exposure, increasing to 2.1 (95% CI = 1.1 to 4.2, 27 exposed cases) for probable or definite exposure, and 13.3 (95% CI = 2.5 to 70, 10 exposed cases) for definite exposure.

Other studies also found the highest risks of nasopharyngeal cancer for individuals with the highest formaldehyde exposure levels (assessed as cumulative exposure, exposure level, or exposure score) (Vaughan *et al.* 1986, Roush *et al.* 1987) and/or longest exposure durations (Vaughan *et al.* 1986, West *et al.* 1993 [after lagging exposures for 10 years]). Risks were also significantly elevated for individuals with longer time since first exposure (West *et al.* 1993) or who died at an older age (Roush *et al.* 1987); risk was increased four-fold for individuals who died after the age of 68 and were probably exposed to high levels of formaldehyde for at least 20 years before death. The associations between formaldehyde exposure and nasopharyngeal cancer remained after adjustment for or consideration of potential confounding by tobacco smoking (Vaughan *et al.* 1986, 2000, West *et al.* 1993, Hildesheim *et al.* 2001) or by exposure to wood dust (West *et al.* 1993, Vaughan *et al.* 2000, Hildesheim *et al.* 2001). Not all of the estimates of increased risk were statistically significant, and some studies (Armstrong *et al.* 2000, Li *et al.* 2006, Hauptmann *et al.* 2009) did not find an association between formaldehyde exposure and nasopharyngeal cancer. However, most of these studies were limited by small numbers of individuals exposed to formaldehyde. The overall consistency of the findings argues against their being attributable to chance.

Excess mortality from nasopharyngeal cancer was found in the NCI cohort of industrial workers exposed to formaldehyde (standardized mortality ratio [SMR] = 2.10, 95% CI = 1.05 to 4.21). Relative risk increased with increasing cumulative exposure ($P_{\text{trend}} = 0.025$ across exposed subjects), peak exposure ($P_{\text{trend}} < 0.001$), and average exposure ($P_{\text{trend}} = 0.066$) (Hauptmann *et al.* 2004). Of the 7 exposed workers who died of nasopharyngeal cancer, all were in the highest peak-exposure category, and 6 were in the highest average-exposure category. Controlling for co-exposure to 11 potential occupational carcinogens and for plant did not alter the exposure-response relationships for nasopharyngeal cancer. Although the cohort included workers in 10 plants, most of the cases of nasopharyngeal cancer occurred in workers in the plant with the largest numbers of workers in the highest formaldehyde exposure category; 46% of workers at Plant 1 were in the highest peak-exposure category, compared with 20.1% of workers in all other plants (Stewart *et al.* 1990, Marsh and Youk 2005). A nested case-control study of nasopharyngeal cancer among workers in Plant 1 found a significantly elevated risk for ever having worked in silversmithing jobs before or after employment at Plant 1; however, silversmithing was not correlated with formaldehyde exposure levels at this plant and therefore was not a confounding factor for formaldehyde exposure (Marsh *et al.* 2007).

No excesses of nasopharyngeal cancer mortality were found in the other large cohort studies (Coggon *et al.* 2003, Pinkerton *et al.* 2004); however, the statistical power of these studies was inadequate to evaluate the risks of rare types of cancer.

Sinonasal Cancer

Sinonasal cancer is a rare cancer, with an annual incidence of about 1 per 100,000, and case-control studies therefore are most useful for evaluation of risk. Sinonasal cancer includes cancers of the paranasal sinus and the nasal cavity; the two major histological types are adenocarcinoma and squamous-cell carcinoma.

The evidence that formaldehyde exposure causes sinonasal cancer comes from consistent findings of increased risk in population-based case-control studies (Olsen *et al.* 1984, Olsen and Asnaes 1986, Hayes *et al.* 1986, Roush *et al.* 1987, Luce *et al.* 1993) and a pooled analysis of 12 case-control studies (Luce *et al.* 2002) that found an excess of sinonasal cancer. In most studies, estimates of increased risk were statistically significant for individuals ever exposed to formaldehyde, or with higher probabilities or levels of exposure (Olsen *et al.* 1984, Olsen and Asnaes 1986, Hayes *et al.* 1986, Luce *et al.* 1993, 2002).

Elevated risks were observed for both adenocarcinoma and squamous-cell carcinoma; however, some studies suggested that adenocarcinoma was more strongly associated with formaldehyde exposure than was squamous-cell carcinoma (Luce *et al.* 1993, 2002). The pooled analysis (which included studies by Hayes *et al.* 1986, Vaughan *et al.* 1986, and Luce *et al.* 1993) was especially informative for evaluating sinonasal cancer, because it had greater statistical power for evaluating risks of rare cancers than did the individual studies, and it used an independent exposure analysis to assess cumulative exposure, rather than relying on the exposure estimates from the original studies. In the pooled analysis, the relative risk of adenocarcinoma increased with increasing cumulative exposure; the odds ratios for individuals with high cumulative exposure were 3.0 (95% CI = 1.5 to 5.7, 91 exposed cases) for men and 6.2 (95% CI = 2.0 to 19.7, 5 exposed cases) for women. Support for a positive exposure-response relationship also comes from a case-control study in France that found higher risks of sinonasal cancer (adenocarcinoma) among individuals with higher average exposure levels and earlier dates of first exposure (Luce *et al.* 1993) and from a case-control study in the Netherlands that found a significantly ($P < 0.05$) higher relative risk of all sinonasal cancer or squamous-cell carcinoma among individuals with "high" exposure than those with "low" exposure (Hayes *et al.* 1986).

Although co-exposure to wood dust is a potential confounding factor for sinonasal cancer, and specifically for adenocarcinoma, increased risk of sinonasal cancer associated with formaldehyde exposure has been found among individuals with little or no exposure to wood dust or after adjustment for wood-dust exposure (Olsen *et al.* 1984, Hayes *et al.* 1986, Olsen and Asnaes 1986). Some studies suggested that co-exposure to formaldehyde and wood dust had an interactive (synergistic) carcinogenic effect (Luce *et al.* 1993, 2002). Two case-control studies did not find an association between formaldehyde exposure and sinonasal cancer; however, one study included only 12 cases of sinonasal cancer in exposed individuals (Vaughan *et al.* 1986), and the other had methodological limitations (Pesch *et al.* 2008). In the cohort studies of industrial workers (including studies of the large NCI, NIOSH, and British cohorts) and professional groups, the statistical power to detect an association between formaldehyde exposure and sinonasal cancer was limited. Nonetheless, a statistically significant excess of sinonasal cancer incidence was found among Danish male workers exposed to formaldehyde and who were unlikely to have been exposed to wood dust (Hansen and Olsen 1995, 1996), and a nonsignificant excess of mortality from sinonasal cancer was found in the NCI cohort. No excess mortality from sinonasal cancer was found in the other cohort studies; however, the statistical power of these studies was inadequate to evaluate the risks of types of cancer.

Lymphohematopoietic Cancer

Evidence that demonstrates an association between formaldehyde exposure and combined lymphohematopoietic cancer is as follows: (1) in the NCI cohort of industrial workers, risk was significantly higher for the highest peak-exposure group than the lowest peak-exposure group, and a positive exposure-response relationship based on peak exposure was found (Beane Freeman *et al.* 2009), (2) increased risks were found in all of the cohort studies of professional groups (NTP 2010), and (3) a significant risk was reported (relative risk [RR] = 1.25, 95% CI = 1.12 to 1.39) in the meta-analysis by Zhang *et al.* (2009). In the NCI cohort study of industrial workers, the risks of Hodgkin's lymphoma and multiple myeloma also were significantly higher among individuals with the highest peak exposure than those with the lowest peak exposure, and a positive exposure-response relationship was found for Hodgkin's lymphoma (Beane Freeman *et al.* 2009). The other studies gave conflicting results for these two types of cancer. In the meta-analyses by Zhang *et al.* (2009), a significant association was found for multiple myeloma, but not for Hodgkin's lymphoma. Because the evidence for these two types of cancer is mainly limited to the NCI cohort study, a causal association is not established.

Increased risks for leukemia (all types combined) were found in all of the professional studies and some of the industrial cohort studies (NTP 2010). Among studies that evaluated subtypes of lymphohematopoietic cancer or leukemia, the strongest associations were observed for myeloid leukemia. For example, in the nested case-control study of embalmers (Hauptman *et al.* 2009), the excess risk of non-lymphoid lymphohematopoietic cancer was explained by a strong association with myeloid cancer, and in other studies, the magnitudes of the effect estimates were higher for myeloid leukemia than for all leukemia or other subtypes of leukemia (Pinkerton *et al.* 2004, Beane Freeman *et al.* 2009, NTP 2010).

The most informative studies for evaluation of the risk of myeloid leukemia are the large cohort studies of industrial workers (the NCI, NIOSH, and British cohorts) and the NCI nested case-control study of lymphohematopoietic cancer in embalmers. Three of these four studies found elevated risks of myeloid leukemia among individuals with high exposure to formaldehyde, as well as positive exposure-response relationships. Confounding is unlikely to explain these increased risks, because there was no evidence of potential confounding in the individual studies, and the increased risks were observed for workers in different industries and occupations (workers at formaldehyde-producing companies, garment workers, and embalmers).

Both the NCI cohort study of industrial workers and the nested case-control study of myeloid leukemia in embalmers found positive exposure-response relationships between myeloid leukemia and peak formaldehyde exposure level. In the study of embalmers, relative risk also increased with increasing duration of employment in embalming ($P_{\text{trend}} = 0.020$) and with increasing average exposure level ($P_{\text{trend}} = 0.058$), in addition to increasing peak exposure level ($P_{\text{trend}} = 0.036$). In analyses using a comparison group of funeral directors with fewer than 500 lifetime embalming, significantly elevated risks of myeloid leukemia (adjusted for smoking) were found among workers with longest duration of employment in embalming (OR = 3.9, 95% CI = 1.2 to 12.5, $P = 0.024$) and the highest cumulative exposure to formaldehyde (OR = 3.1, 95% CI = 1.0 to 9.6, $P = 0.047$). In addition, elevated risk estimates of borderline statistical significance were found for those who had performed the largest numbers of embalming (OR = 3.0, 95% CI = 1.0 to 9.2, $P = 0.057$). In a 1994 update of the NCI cohort study (based on reanalyses that included additional deaths and recoding of deaths), risk was significantly higher for the highest category of peak exposure (RR = 2.79, 95% CI = 1.08 to 7.21) than for the lowest exposure category, and risk increased with increasing peak ex-

posure ($P_{\text{trend}} = 0.02$) (Beane Freeman *et al.* 2009). In a 2004 follow-up study, elevated risk estimates were still observed, but the magnitude of the association between formaldehyde exposure and myeloid leukemia decreased as time since the last known exposure increased to at least 24 years. This pattern is consistent with a follow-up period longer than the optimal latency period for cancer, as has been seen with other leukemia-inducing agents (Silver *et al.* 2002). Controlling for co-exposure to 11 potential occupational carcinogens did not alter the findings for myeloid leukemia.

In the NIOSH cohort study of garment workers, elevated risks of death from myeloid leukemia were found for all workers and for subgroups of workers with the highest exposure or longest latency. SMRs were highest among workers with longer exposure duration (≥ 10 years), longer time since first exposure (≥ 20 years), or earlier year of first exposure (before 1963, when exposure levels were higher). In an analysis that included all causes of death listed on the death certificate (rather than just the underlying cause), the risk of death from myeloid leukemia was significantly increased for workers who had been exposed for at least 10 years (SMR = 2.24, 95% CI = 1.02 to 4.25, 9 deaths) and was concentrated among workers with time since first exposure of at least 20 years who had been exposed for at least 10 years (SMR = 2.55, 95% CI = 1.10 to 5.03, 8 deaths) (Pinkerton *et al.* 2004). In the large cohort of British chemical workers, no increased risk of leukemia was found for formaldehyde exposure. However, this study did not evaluate myeloid leukemia specifically, and exposure-response analyses were limited; exposure was assessed as "high" or "ever," and the assessment was not calendar-year-specific (Coggon *et al.* 2003). Only one case-control study reported specific findings for myeloid leukemia; an excess risk was found for chronic (but not acute) myeloid leukemia, based on small numbers of formaldehyde-exposed individuals with leukemia (Blair *et al.* 2001).

Although several meta-analyses have been published, none has included the nested case-control study of myeloid leukemia among embalmers by Hauptmann *et al.* (2009). The most informative meta-analysis (Zhang *et al.* 2009) found a significantly elevated risk of myeloid leukemia (summary RR = 1.90, 95% CI = 1.31 to 2.76, $P = 0.001$) across studies using risk estimates, when available, for workers with the highest formaldehyde exposure. A meta-analysis by Bachand *et al.* (2010) did not find a significantly elevated risk of myeloid leukemia (summary RR = 1.09, 95% CI = 0.84 to 1.40); however, this analysis did not include the proportionate-mortality cohort studies (studies that compared the proportions of deaths between the study population and a reference population), which reported increased risks of myeloid leukemia. Bosetti *et al.* (2008) found an elevated risk of leukemia across studies of professional groups but not across studies of industrial workers. This finding is consistent with observations that embalmers have longer duration of exposure and higher cumulative exposure and are more likely to be exposed to peak exposure levels greater than 4 ppm than are industrial workers, and that cancer risk is associated with peak levels of exposure to formaldehyde (Hauptmann *et al.* 2009).

Cancer at Other Tissue Sites

The association between formaldehyde exposure and cancer at other tissue sites is weaker than for nasal or lymphohematopoietic cancer (see NTP 2010 for a review of the studies). Increased risks of head and neck cancers (of the buccal cavity, pharynx, larynx, or combinations of these sites) were observed in many of the cohort and case-control studies, but most were not statistically significant, and there were no consistent findings of higher risk among the individuals with the highest exposure levels. An excess of brain cancer mortality was found in all studies of professional groups, but not in the cohort stud-

ies of industrial workers, and no positive exposure-response relationship was found in the NCI nested case-control study of brain cancer among embalmers. Findings for lung cancer were inconsistent, and the data were inadequate to evaluate the association between formaldehyde exposure and cancer at other tissue sites.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of formaldehyde from studies in experimental animals. Formaldehyde caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Long-term inhalation exposure to formaldehyde caused nasal tumors, both benign (polypoid adenoma) and malignant (predominantly squamous-cell carcinoma but also adenocarcinoma and carcinoma) in male and female F344 rats (Kerns *et al.* 1983, Monticello *et al.* 1996, Kamata *et al.* 1997), male Sprague-Dawley rats (Sellakumar *et al.* 1985), and male B6C3F₁ mice (Kerns *et al.* 1983). Nasal tumors were also observed after short-term exposure (13 weeks) in male Wistar rats (Feron *et al.* 1988). Although the increased incidences of nasal tumors in mice and in the short-exposure study in rats were not statistically significant, they were considered to be biologically significant because of the rarity of this type of tumor.

Long-term exposure of adult rats to formaldehyde in drinking water caused benign tumors of the forestomach (squamous-cell papilloma) in male Wistar rats (Takahashi *et al.* 1986) and testes (interstitial-cell adenoma) (Soffritti *et al.* 2002, statistics reported in IARC 2006) in male Sprague-Dawley rats. Increased incidences of intestinal tumors (primarily leiomyosarcoma, which are rare malignant tumors of the muscle of the intestine) were observed in female Sprague-Dawley rats exposed to formaldehyde *in utero* starting on gestational day 13 and throughout life via the drinking water (Soffritti *et al.* 1989, statistics reported in IARC 2006). Leiomyosarcoma of the stomach and intestines was also observed in the formaldehyde-exposed groups, but not the concurrent control groups (untreated animals and control animals given methanol), in Sprague-Dawley rats exposed as adults. Although the findings were not statistically significant, they are of concern because of the rarity of these tumors. Hemolymphoreticular tumors (combined types) in rats of both sexes also were significantly increased after long-term exposure of adults; however, it is unclear whether these tumors were exposure-related, because of limitations in the reporting of these tumors (Soffritti *et al.* 2002, IARC 2006). In tumor promotion and co-carcinogenicity studies, formaldehyde was shown to promote tumors of the stomach and lung in rats (NTP 2010).

Other Relevant Data

Formaldehyde exposure occurs from both endogenous and exogenous sources. It is rapidly absorbed after inhalation and oral exposure; however, it is poorly absorbed via the skin (NTP 2010). The half-life of formaldehyde in the plasma of rats and monkeys is about 1 to 1.5 minutes (McMartin *et al.* 1979, IARC 2006). Differences in breathing patterns across species may affect differences in absorption and distribution. In rats, almost all inhaled formaldehyde is absorbed in the nasal passage, whereas in primates, some absorption occurs in the trachea and proximal regions of the major bronchi (Chang *et al.* 1983, Heck *et al.* 1983, Monticello *et al.* 1989, Casanova *et al.* 1991). The metabolism of formaldehyde is similar in all mammalian species studied (IARC 2006). Although pure formaldehyde is a gas at room temperature, it hydrates rapidly and is in equilibrium with its hydrated form, methanediol (Fox 1985); at room and body temperatures, the dominant form is methanediol. Formaldehyde is rapidly metabolized by glutathione-dependent formaldehyde dehydrogenase (also known as alcohol dehydrogenase 5, ADH5) and *S*-formyl-glutathione

hydrolase to formic acid, which enters the one-carbon pool and can be either excreted in the urine or oxidized to carbon dioxide and exhaled. ADH5 has been detected in all human tissues at all stages of development, from embryo through adult (Thompson *et al.* 2009). Although formaldehyde is rapidly metabolized, it is an electrophile that reacts with a variety of endogenous molecules, including glutathione, proteins, nucleic acids, and folic acid (NTP 2010).

Studies on Mechanisms of Carcinogenesis

The mechanisms by which formaldehyde causes cancer are not completely understood and most likely involve several modes of action. Formaldehyde exposure is associated with key events related to carcinogenicity, such as DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, epigenetic effects (binding to lysine residues of histones), glutathione depletion, oxidative stress, and cytotoxicity-induced cellular proliferation (Lu *et al.* 2008, Guyton *et al.* 2009, NTP 2010). Understanding of the mechanisms is more advanced for nasal tumors than for lymphohematopoietic cancer. There is evidence for a genotoxic mode of action for both types of cancer. Formaldehyde is a direct-acting genotoxic compound and has given positive results for almost all genetic end points evaluated in bacteria, yeast, fungi, plants, insects, nematodes, and cultured mammalian cells. It caused base-pair gene mutations in *Salmonella typhimurium* and DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, DNA single-strand breaks, unscheduled DNA synthesis, inhibition of DNA repair, gene mutations, cell transformation, and cytogenetic effects (sister chromatid exchange, chromosomal aberrations, and micronucleus formation) in cultured mammalian cells (NTP 2010). It was also genotoxic in experimental animals and humans exposed *in vivo* (discussed below). There is some evidence to suggest that the Fanconi anemia complementation group (BRCA/FANC) response pathway may be important in the prevention of DNA damage from formaldehyde exposure (Zhang *et al.* 2010a). Cells deficient in FANC genes were hypersensitive to formaldehyde exposure and had increased frequencies of micronuclei and cancer (Speit *et al.* 2000, Ridpath *et al.* 2007).

Nasal Cancer

Mechanistic studies in humans and experimental animals support the findings that formaldehyde causes nasopharyngeal and sinonasal cancer in humans. Formaldehyde causes genetic damage to the nasal tissues of both experimental animals and humans exposed by inhalation. DNA-protein crosslinks were detected in the nasal mucosa of rats exposed to formaldehyde (Casnaova *et al.* 1989, 1994, NTP 2010) and in the nasal turbinates (Heck *et al.* 1989, Casanova *et al.* 1991) and the respiratory tract (larynx, trachea, carina, and bronchi) (Casanova *et al.* 1991) of rhesus monkeys exposed to formaldehyde, which correspond to the observed tumor sites in humans (nasal and nasopharyngeal). In dose-response studies in rats, DNA crosslinks were correlated with tumor incidence (Liteplo and Meek 2003). DNA-protein crosslinks were also correlated with the severity and anatomical location of proliferative nasal lesions in rhesus monkeys (Casanova *et al.* 1991). *N*²-hydroxymethyl-deoxyguanosine (dG) DNA monoadducts and dG-dG crosslinks were found in rat nasal mucosa (Lu *et al.* 2010). Mutations in the *p53* tumor-suppressor gene (at G:C base pairs) were found in formaldehyde-induced nasal squamous-cell carcinomas in rats, and all of the identified codon mutations have also been found in human cancers (Recio *et al.* 1992). In humans, formaldehyde exposure was associated with higher levels of serum *p53* protein (wild-type and mutant *p53* protein), and serum *p53* protein levels were positively correlated with mutant *p53* protein levels. Higher levels of DNA-protein crosslinks in lymphocytes were significantly associated with increased risk of higher serum *p53* levels

(Shaham *et al.* 2003). However, *p53* mutations were not observed in rat nasal mucosa exposed to formaldehyde for 13 weeks, suggesting that they may be a later event in the progression of cancer (Meng *et al.* 2010). Numerous studies of industrial workers and professional groups exposed to formaldehyde found that formaldehyde exposure increased the frequency of micronuclei in the nasal epithelium and buccal epithelium (Ballarin *et al.* 1992, Suruda *et al.* 1993, Titenko-Holland *et al.* 1996, Kitaeva *et al.* 1996, Ying *et al.* 1997, Burgaz *et al.* 2001, 2002, Ye *et al.* 2005).

Inhalation-exposure studies in experimental animals have shown that airway deposition and cytotoxicity-induced cellular proliferation also are important factors in the carcinogenicity of formaldehyde to nasal cells. In rats, regional formaldehyde flux (as estimated by computational fluid dynamic models) was correlated with the anatomical distribution of formaldehyde-induced lesions (squamous metaplasia) (Kimbell *et al.* 1997) and DNA-protein crosslinks (Hubal *et al.* 1997). Inhalation of formaldehyde by rodents causes cytotoxicity of the respiratory epithelium (rhinitis, epithelial dysplasia, and squamous metaplasia) (Chang *et al.* 1983, Monticello *et al.* 1991, 1996), which can result in cellular proliferation and the promotion of chemically induced or spontaneous mutations. Cellular proliferation has been shown to be correlated with local nasal tumor incidence (Monticello *et al.* 1989, 1996). Formaldehyde exposure also causes cytotoxicity and cellular proliferation at anatomical sites that are not thought to be the origin of the squamous-cell carcinoma, suggesting that factors other than cellular proliferation play a role in formaldehyde-induced nasal cancers (Monticello *et al.* 1991).

Leukemia

Lymphohematopoietic cancers are a heterogeneous group of cancers that arise from damage to stem cells during hematopoietic and lymphoid development (Greaves 2004). Blood cells arise from a common stem cell, which forms two progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. Most agents known to cause leukemia are thought to do so by directly damaging stem cells in the bone marrow. In order for a stem cell to become malignant, it must acquire genetic mutations and genomic instability (Zhang *et al.* 2010a). Because formaldehyde is highly reactive and rapidly metabolized, a key question is how it can reach the bone marrow or cause toxicity or genotoxicity at distal sites. The endogenous concentration in the blood of humans, monkeys, and rats is about 2 to 3 µg/g, and the concentration does not increase after inhalation of formaldehyde from exogenous sources (Heck *et al.* 1985, Casanova *et al.* 1988, Heck and Casanova *et al.* 2004). Moreover, *N*²-hydroxymethyl-dG-DNA adducts have not been detected at distal sites in rats (such as the bone marrow, white blood cells, lung, spleen, liver, or thymus) (Lu *et al.* 2010). For these reasons, the plausibility of formaldehyde's causing cancer at distal sites, such as myeloid leukemia, has been questioned (Golden *et al.* 2006, Pyatt *et al.* 2008).

However, systemic effects have been observed after inhalation or oral exposure, and although the mechanisms by which formaldehyde causes myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced. These include (1) theoretical mechanisms for the distribution of formaldehyde to distal sites and (2) proposed mechanisms of leukemogenesis that do not require formaldehyde to reach the bone marrow. In addition, there is some evidence that formaldehyde causes adverse hematological effects in humans.

Systemic Effects Observed After Inhalation or Oral Exposure

Serum levels of formaldehyde-albumin adducts were significantly higher in laboratory workers exposed to high levels of formaldehyde

than in workers exposed at lower levels (Pala *et al.* 2008). In addition, levels of formaldehyde-DNA adducts in leukocytes were significantly higher in smokers than in nonsmokers; however, it is not known whether the source of the adducts was formaldehyde in tobacco smoke or from metabolism of a tobacco-specific compound (Wang *et al.* 2009). Numerous studies in humans and experimental animals have demonstrated that inhaled formaldehyde can cause toxicity, genotoxicity, and cancer at distal sites. In humans, formaldehyde exposure has been associated with (1) hematological toxicity (see below), (2) genotoxic damage in lymphocytes, including DNA-protein crosslinks, DNA strand breaks (Shaham *et al.* 2003, Costa *et al.* 2008), micronucleus formation (Suruda *et al.* 1993, He *et al.* 1998, Orsière *et al.* 2006, Costa *et al.* 2008), and chromosomal aberrations (albeit not in all studies) (Jakab *et al.* 2010, NTP 2010), and (3) myeloid leukemia (discussed above).

In experimental animals, inhaled formaldehyde was associated with toxicity to the liver in several species (Beall and Ulsamer 1984, Cikmaz *et al.* 2010) and the nervous system (neurobehavioral changes and cellular and biochemical changes in the hippocampus) in mice and rats (Aslan *et al.* 2006, Sarsilmaz *et al.* 2007, Lu *et al.* 2008, Songur *et al.* 2010). In rats, it was also associated with toxicity to the testes (morphometric changes in the seminiferous epithelium) (Özen *et al.* 2005, Golalipour *et al.* 2007), spleen (morphometric alterations in the white pulp) (Golalipour *et al.* 2008), and thyroid gland (lower weight and changes in levels of thyroid hormones) (Patel *et al.* 2003). The mechanisms for systemic toxicity in experimental animals are not known, but oxidative stress has been suggested to play a role in testicular toxicity and neurotoxicity. In general, most studies did not present information on whether respiratory injury was observed with formaldehyde exposure.

Inhaled formaldehyde also caused DNA single-strand breaks in the liver and lymphocytes of male rats (Im *et al.* 2006), dominant lethal mutations in rats (Kitaeva *et al.* 1990), and heritable mutations in mice (Liu *et al.* 2009); however, most studies found no cytogenetic effects (NTP 2010). Findings for chromosomal aberrations in bone marrow of rats exposed to inhaled formaldehyde are conflicting; aberrations were found by Kitaeva *et al.* (1990), but not by Dallas *et al.* (1992). Prenatal exposure of rats to formaldehyde by intraperitoneal injection caused DNA-protein crosslinks and DNA strand breaks in the fetal liver (Wang and Liu 2006), and oral exposure to formaldehyde caused testicular tumors (Soffritti *et al.* 2002).

Theoretical Mechanisms for the Distribution of Formaldehyde to Distal Sites

The mechanisms by which formaldehyde causes toxicity at distal sites are unknown. The formation of methanediol (discussed above) from formaldehyde helps to explain how a reactive chemical could be distributed and undergo metabolism throughout the body (Fox 1985, Matubayasi *et al.* 2007). The upper respiratory tissues are covered by an aqueous mucous membrane, through which formaldehyde could be transported as methanediol (Georgieva *et al.* 2003). In addition, formaldehyde reacts reversibly with a variety of endogenous molecules, including glutathione, amino acids, and folic acid (Heck *et al.* 1982). These reversible products may be transported from the portal of entry to reach remote sites where free formaldehyde can then be released. However, there is no experimental evidence to support these potential mechanisms.

Other Potential Mechanisms of Formaldehyde-Induced Leukemia

Zhang *et al.* (2009) proposed that formaldehyde could also cause leukemia by other mechanisms that do not involve direct damage to the bone marrow: (1) formaldehyde could damage stem cells circulating

in the blood, which travel to the bone and become initiated leukemia cells, or (2) it could damage stem cells that reside in the nasal turbinates or olfactory mucosa. Hematopoietic stem cells have been identified in the peripheral circulation and can circulate back to the bone marrow (Fritsch *et al.* 1996). The findings of cytogenetic damage in circulating lymphocytes of formaldehyde-exposed workers (discussed above) support the first hypothesis, and the findings of cytogenetic damage (micronuclei) in nasal tissue support the second. High levels of chromosomal aberrations and micronuclei are associated with increased cancer risks in otherwise healthy individuals (Bonassi *et al.* 2008, Murgia *et al.* 2008). Moreover, Murrell *et al.* (2005) found that the olfactory epithelium of the nasal passages of rats contained multipotent stem/progenitor cells that were able to repopulate the hematopoietic tissues of irradiated rats and to form progenitor cells of multiple lineages.

Hematotoxicity

Damage to hematopoietic stem or progenitor cells would result in adverse hematological effects, which have been reported in some, but not all, studies in humans. However, no adverse hematological effects have been reported in subchronic or chronic studies in experimental animals (Dean *et al.* 1984, Appelman *et al.* 1988, Kamata *et al.* 1997). Zhang *et al.* (2010b) found that formaldehyde-exposed workers had lower counts of white blood cells, granulocytes, platelets, red blood cells, and lymphocytes than did non-exposed workers. Furthermore, myeloid progenitor cells cultured from the blood of a subset of workers showed an increased frequency of aneuploidy of chromosomes 7 (monosomy) and 8 (trisomy). Monosomy 7 and trisomy 8 are associated with myeloid leukemia (Johnson and Cotter 1997, Paulsson and Johansson 2007). In addition, formaldehyde exposure *in vitro* caused a decrease in colony-forming progenitor cells (erythroid burst-forming units, erythroid colony-forming units, and granulocyte, erythrocyte, monocyte, and megakaryocyte colony-forming units). A review of the Chinese literature reported that decreased white blood cell counts were observed in most studies of formaldehyde-exposed workers; in the largest study, exposed workers had higher percentages of blood abnormalities (decreased white blood cell and platelet counts and abnormal hemoglobin levels) (Tang *et al.* 2009).

Properties

Formaldehyde is the simplest aldehyde. It exists at room temperature as a nearly colorless gas with a pungent, suffocating odor (ATSDR 1999, HSDB 2009). It is soluble in water, ether, acetone, and benzene. The primary form of formaldehyde in dilute aqueous solutions is its monomeric hydrate methylene glycol (methanediol), and the primary forms in concentrated solutions are oligomers and polymers of polyoxymethylene glycols. Commercially, formaldehyde is most often available as 30% to 50% (by weight) aqueous solutions of the hydrated form, which is commonly referred to as formalin (IARC 2006). Formalin contains added stabilizers, generally up to 15% methanol or lower concentrations (usually several hundred milligrams per liter) of various amine derivatives. In the absence of stabilizers, formaldehyde in solution oxidizes slowly to form formic acid and polymerizes to form oligomers, including paraformaldehyde, a polymer with 8 to 100 units of formaldehyde (HSDB 2009). Formaldehyde can also exist in solid form as 1,3,5-trioxane, a cyclic trimer. Formaldehyde gas is generally stable in the absence of water, but it is flammable and can be ignited by heat, sparks, or flame. Vapors form explosive mixtures with air. Formaldehyde gas reacts violently with strong oxidizing agents and with bases and reacts explosively with nitrogen dioxide at around 180°C (356°F) (Akron 2009). Physical and chemical properties of formaldehyde are listed in the following table.

Property	Information
Molecular weight	30.0 ^a
Specific gravity	0.815 at -20°C/4°C ^b
Melting point	-92°C ^a
Boiling point	-19.5°C ^a
Log K_{ow}	0.35 ^a
Water solubility	400 g/L at 25°C ^a
Vapor pressure	3,890 mm Hg at 25°C ^a
Vapor density relative to air	1.067 ^a
Dissociation constant (pK _a)	13.27 at 25°C ^a

^aHSDB 2009, ^bO'Neil *et al.* 2006.

Use

Formaldehyde has numerous industrial and commercial uses; it is used in industrial processes primarily as a solution (formalin) or solid (paraformaldehyde or trioxane). The predominant use (~55% of total consumption) is in the production of industrial resins (mainly urea-formaldehyde, phenol-formaldehyde, polyacetal, and melamine-formaldehyde resins) (Bizzari 2007). These resins are used to manufacture numerous commercial products, including adhesives and binders for composite wood products, pulp and paper products, plastics, and synthetic fibers, and in textile finishing. Another major use (~29%) is as a chemical intermediate to produce other chemicals. Various agricultural uses (~5%), paraformaldehyde production (~3%), and production of chelating agents (~3%) account for most of the remaining uses. The remaining 5% of formaldehyde goes toward other uses that may still be important for human exposure, including its use as a disinfectant or antimicrobial agent in various consumer products, as a medical treatment for some skin conditions, as a tissue preservative for pathologists and embalmers, and as a biocide and preservative in food and cosmetic products. Formaldehyde is registered as a materials preservative for use in consumer products such as laundry detergents, general-purpose cleaners, and wallpaper adhesives (ATSDR 1999, IARC 2006, EPA 2008). The main uses for paraformaldehyde are as foundry resins and in applications where the presence of water could interfere with a production process. Paraformaldehyde is also used as an antimicrobial agent for in-drawer fumigation of hair-cutting equipment and as a mildewcide in closets and unoccupied vacation homes (EPA 2008).

Production

Formaldehyde is produced by catalytic oxidation of methanol via a silver or metal-oxide catalyst process. Annual production of formaldehyde in the United States increased from about 0.9 million metric tons (1 million tons) in 1960 to 4.5 million metric tons (5 million tons) in 2006 (Bizzari 2007). In 2009, formaldehyde was produced by 12 companies and their subsidiaries at 39 U.S. manufacturing plants (Bizzari 2007, SRI 2009), and paraformaldehyde and trioxane each were produced at one U.S. manufacturing plant (SRI 2009). Formaldehyde was available from 36 U.S. suppliers, paraformaldehyde from 25, and trioxane from 11. Internationally, formaldehyde was available from 152 suppliers in 25 countries, paraformaldehyde from 59 in 15 countries, and trioxane from 21 in 9 countries (ChemSources 2009). Because of transportation and storage issues associated with formaldehyde, it usually is produced close to the point of consumption; therefore, international trade in formaldehyde is minimal (less than 2% of worldwide production) (Bizzari 2007). In 2006, U.S. imports of formaldehyde were about 10,000 metric tons (11,000 tons), and U.S. exports were about 14,000 metric tons (15,400 tons).

Exposure

Humans are exposed to formaldehyde in the environment and in the workplace. Formaldehyde concentrations in the environment generally are reported in parts per billion, but exposure levels are much higher in the workplace, occurring in the range of parts per million. Formaldehyde is also produced endogenously in humans and animals.

Environmental Exposure

Formaldehyde is ubiquitous in the environment and has been detected in indoor and outdoor air, soil, food, treated and bottled drinking water, surface water, and groundwater (NTP 2010). The general population can be exposed to formaldehyde primarily from breathing indoor or outdoor air, from tobacco smoke, from use of cosmetic products containing formaldehyde, and, to a more limited extent, from ingestion of food and water. For the general population, the major sources of airborne formaldehyde exposure include combustion sources, off-gassing from numerous construction and home-furnishing products, and offgassing from consumer goods. Formaldehyde gas is produced from the oxidation or incomplete combustion of organic material. Combustion sources include automobiles and other internal combustion engines, power plants, incinerators, refineries, forest fires, wood stoves, and cigarettes. Formaldehyde is also formed in the early stages of decomposition of plant residues in soil (IARC 2006). Formaldehyde can be produced secondarily in air via photochemical reactions involving virtually all classes of hydrocarbon pollutants; in some instances, secondary production may exceed direct air emissions. Formaldehyde concentrations in outdoor air generally range from 0 to 100 ppb (0 to 0.1 ppm) and usually are less than 10 ppb (0.01 ppm); daily exposure from outdoor air has been estimated at 0.1 mg or less (HSDB 2009).

Formaldehyde levels can be higher in indoor air than in outdoor air. Important determinants of indoor air levels include the sources of the formaldehyde, the age of the source materials, temperature, humidity, and ventilation rates (IARC 2006). Although daily formaldehyde exposure from residential indoor air in conventional homes has been reported to range from 0.5 to 2.0 mg, daily exposure in a prefabricated home was as high as 10 mg (Fishbein 1992). Temporary housing provided by the Federal Emergency Management Agency as shelter for residents of Louisiana and Mississippi displaced by Hurricanes Katrina and Rita had formaldehyde concentrations ranging from 3 to 590 ppb (0.003 to 0.59 ppm) (CDC 2008, 2009). Most of the housing was at least two years old at the time of sampling, which occurred during the winter months. Formaldehyde levels were higher in travel trailers than park models or mobile homes. Higher concentrations of formaldehyde than were found by the Centers for Disease Control and Prevention have been reported by others (for example, see COGR 2007). There are no federal guidelines for formaldehyde levels in residential housing for indoor air quality (CDC 2008).

Daily exposure to formaldehyde was estimated at up to 2 mg from smoking 20 cigarettes per day, up to 3.5 mg from environmental tobacco smoke in the home, and 2.8 mg from environmental tobacco smoke in the workplace (WHO 2000).

The general population could also be exposed to formaldehyde by handling consumer products that contain formaldehyde as an antimicrobial agent (such as laundry detergents, wallpaper adhesive, or sanitizers) or from its use as a mildewcide for clothing and linens or in vacation homes (EPA 2008). Although formaldehyde *per se* now is rarely used in cosmetics, the use of formaldehyde releasers is common. An analysis of data from the U.S. Food and Drug Administration's Voluntary Cosmetic Registration Program Database indicated that nearly 20% (6,463 of 33,212) of cosmetic products contained formaldehyde (including formalin) or any of eight formaldehyde-releasing

preservatives (benzylhemiformal, 5-bromo-5-nitro-1,3-dioxane, 2-bromo-2-nitropropane-1,3-diol, diazolidinyl urea, 1,3-dimethylol-5,5-dimethylhydantoin, imidazolidinyl urea, quaternium-15, or sodium hydroxymethylglycinate) (De Groot and Veenstra 2010, De Groot *et al.* 2010). Absorption of formaldehyde from hand cream or suntan lotion was estimated at up to 0.1 mg for a typical application, assuming 5% absorption through the skin (ATSDR 1999). Other products that often contain formaldehyde releasers are industrial and household cleaning agents, soaps, shampoos, paints, lacquers, and cutting fluids (WHO 2002).

Food and water contain measureable concentrations of formaldehyde (WHO 2002, Mutsuga *et al.* 2006), but the significance of ingestion as a source of formaldehyde exposure for the general population is questionable. Formaldehyde in food exists mostly in a bound form (IPCS 1989, Fishbein 1992), and it is considered to be unstable in aqueous solution (ATSDR 1999). Formaldehyde present in food can occur naturally or through inadvertent contamination; it can also be added as a preservative, disinfectant, or bacteriostatic agent and can result from cooking or smoking of foods (Howard 1989, IPCS 1989, ATSDR 1999). Generally, higher levels were reported in fish, seafood, and smoked ham than in other foods (Li *et al.* 2007, NTP 2010). Formaldehyde in treated drinking water occurs primarily through the oxidation of organic matter during ozonation or chlorination; concentrations of up to 30 µg/L were reported (WHO 2005). Formaldehyde can also be present in the water before treatment; it was found in 16 of 35 influent samples at concentrations ranging from 1.2 to 13 µg/L (Krasner *et al.* 1989).

Formaldehyde is an essential metabolic intermediate in the biosynthesis of purines, thymidine, and some amino acids. It is also produced via metabolism of some amino acids and a variety of xenobiotics, such as drugs, food additives, and other environmental chemicals (IARC 2006). The endogenous concentration of formaldehyde in the blood of humans, monkeys, and rats is approximately 2 to 3 µg/g (Heck *et al.* 1985, Casanova *et al.* 1988).

Occupational Exposure

In occupational environments, formaldehyde occurs mainly as a gas; however, formaldehyde particulates can be inhaled when paraformaldehyde or powdered resins are used or when formaldehyde adsorbs to other particles, such as wood dust (IARC 1995). Workers may also be exposed through contact of formalin solutions or liquid resins with the skin or eyes. Occupational exposure to formaldehyde is highly variable and can occur in numerous industries, including the manufacture of formaldehyde and formaldehyde-based resins, wood-composite and furniture production, plastics production, embalming, foundry operations, fiberglass production, construction, agriculture, firefighting, and histology, pathology, and biology laboratories, among others. In the past, the highest continuous exposure levels were measured during the varnishing of furniture and wooden floors, during the finishing of textiles, in the garment industry, during the treatment of furs, and in certain jobs in manufactured board mills and foundries. Short-term exposure to high levels of formaldehyde has been reported for embalmers, pathologists, and paper workers. Lower levels of exposure have usually been reported for the manufacture of synthetic vitreous fibers, abrasives, and rubber, and in formaldehyde production (IARC 2006). It has been suggested that because formaldehyde is ubiquitous, occupational exposure occurs in all workplaces (WHO 2002). Daily formaldehyde intake from occupational exposure has been estimated at up to 8 mg (WHO 2000).

In the United States, high exposure levels were reported for formaldehyde-based resin production (mean concentrations of up to 14.2 ppm), plastic product production (up to 38.2 ppm) (Stewart

et al. 1987), embalming (up to 2.6 ppm) (Stewart *et al.* 1992), biology teaching laboratories (up to 8.3 ppm) (EPA 1981), and pathology autopsy laboratories (up to 4.35 ppm) (Moseley *et al.* 1979). Using formaldehyde exposure data from the Occupational Safety and Health Administration (OSHA) air sampling database for various U.S. industries from 1979 to 2001, Lavoué *et al.* (2008) found the highest estimated relative indices of exposure based on time-weighted-average exposure data for the reconstituted wood products and lumber and wood products industries. The highest estimated relative indices of exposure based on short-term exposure data (aggregated short-term, peak, and ceiling exposure levels) were for the reconstituted wood products industry and funeral services and crematories.

In the late 1980s, OSHA estimated that over 2 million U.S. workers were exposed to formaldehyde, about 45% of whom worked in the garment industry (USDOL 2009). OSHA estimated that about 1.9 million workers were exposed to formaldehyde at concentrations between 0.1 and 0.5 ppm, 123,000 at 0.5 to 0.75 ppm, and 84,000 at 0.75 to 1 ppm (WHO 2002). No current data were found for occupational exposure to formaldehyde in the United States.

Regulations

Coast Guard, Department of Homeland Security

46 CFR 150 and 151 detail procedures for shipping formaldehyde, formaldehyde solution, and 1,3,5-trioxane with incompatible chemicals.

Minimum requirements have been established for safe transport of formaldehyde solutions on ships and barges.

Consumer Product Safety Commission (CPSC)

Formaldehyde and products containing 1% or more formaldehyde are considered "strong sensitizers" and must display a warning label.

Department of Agriculture (USDA)

Limits have been established for the amount of residual formaldehyde in inactivated bacterial products and killed-virus vaccines.

Department of Housing and Urban Development (HUD)

All plywood and particleboard materials bonded with a resin system or coated with a surface finish containing formaldehyde shall not exceed the following emission levels when installed in manufactured homes: 0.2 ppm for plywood and 0.3 ppm for particleboard.

Manufactured homes must prominently display a notice which provides information on formaldehyde sources, levels, health effects, and remedial actions to reduce indoor levels.

Department of Transportation (DOT)

Formaldehyde, formalin, and paraformaldehyde are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials, as prescribed in 49 CFR 172.

Environmental Protection Agency (EPA)

Clean Air Act

Clean-Fuel Vehicles: Formaldehyde emissions limits have been established for various classes of clean-fuel vehicles.

Control of Emissions from New and In-Use Highway Vehicles and Engines: Formaldehyde emissions limits have been established for various classes of vehicles.

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of formaldehyde is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb.

Regulation of Fuels and Fuel Additives: Under reformulated gasoline certification requirements, formaldehyde emissions levels must not be exceeded.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Formaldehyde and paraformaldehyde are listed as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Formaldehyde reportable quantity (RQ) = 100 lb.

Paraformaldehyde reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 500 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of formaldehyde = U122, K009, K010, K038, K040, K156, K157.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Numerous formaldehyde-based chemicals may be used as components of adhesives and coatings in packaging, transporting, or holding food provided that conditions prescribed in 21 CFR 175 are met.

Numerous formaldehyde-based chemicals may be safely used as articles intended for use in contact with food provided that conditions prescribed in 21 CFR 177 are met.

Numerous formaldehyde-based chemicals may be used in the production of paper products intended for use in producing, processing, preparing, treating, packaging, transporting, or holding food provided that conditions prescribed in 21 CFR 176 are met.

Formaldehyde and formaldehyde-based chemicals may be used as adjuvants, production aids, and sanitizers that come in contact with foods provided that conditions prescribed in 21 CFR 178 are met.

Formaldehyde-based ion-exchange resins may be used in the treatment of food provided that conditions prescribed in 21 CFR 173 are met.

Formaldehyde may be safely used in the manufacture of animal feeds in accordance with conditions prescribed in 21 CFR 573.460.

Formalin, containing approximately 37% formaldehyde gas by weight, can be used in environmental waters for the control of fungi and parasites for certain finfish and shellfish as prescribed in 21 CFR 529.

Mine Safety and Health Administration

Engine exhaust from mobile diesel-powered transportation equipment must be diluted with air so that the mixture contains no more than 0.001% by volume of aldehydes, calculated as equivalent formaldehyde.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.75 ppm (0.92 mg/m³) (8-h TWA).

Short-term exposure limit (STEL) = 2 ppm (2.46 mg/m³) (15-min exposure).

Action level = 0.5 ppm (0.61 mg/m³) (8-h TWA).

Comprehensive standards have been developed for occupational exposure to formaldehyde gas, its solutions, and materials that release formaldehyde. These standards identify the permissible exposure limits and prescribe requirements for monitoring exposures, using respiratory protection, conducting medical evaluations, housekeeping, and other activities at 29 CFR 1910.1048 (General Industry), 29 CFR 1926.1148 (Construction Industry), and 29 CFR 1915.1048 (Shipyards).

Requirements for preventing or minimizing the consequences of catastrophic releases of toxic, reactive, flammable, or explosive chemicals are prescribed in 29 CFR 1910.119; the threshold quantity (TQ) for formaldehyde is 1,000 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 0.3 ppm (0.37 mg/m³).

Listed as a suspected human carcinogen.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.016 ppm (0.02 mg/m³) (10-h TWA).

Immediately dangerous to life and health (IDLH) limit = 20 ppm (24.56 mg/m³).

Ceiling recommended exposure limit = 0.1 ppm (0.12 mg/m³) (15-min exposure).

Listed as a potential occupational carcinogen.

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Furan

CAS No. 110-00-9

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

Furan is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to furan caused tumors at several different tissue sites in mice and rats. Administration of furan by stomach tube for up to 2 years caused benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice and rats of both sexes. It also caused bile-duct cancer (cholangiocarcinoma) and mononuclear-cell leukemia in rats of both sexes and benign adrenal-gland tumors (pheochromocytoma) in mice of both sexes (NTP 1993). Similar administration of furan to male rats for 9 to 13 weeks caused bile-duct cancer (cholangiocarcinoma) by 16 months after the end of exposure (Maronpot *et al.* 1991, Elmore and Sirica 1993). Since furan was listed

in the *Eighth Report on Carcinogens*, an additional study in mice has been identified. Intraperitoneal injection of furan caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in newborn male mice (Johansson *et al.* 1997).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to furan.

Studies on Mechanisms of Carcinogenesis

In bacteria, furan caused gene mutations in *Salmonella typhimurium* strain TA100 (Lee *et al.* 1994) and in *Escherichia coli* containing bacteriophage T7 (Ronto *et al.* 1992), but not in *S. typhimurium* strains TA98 (Lee *et al.* 1994), TA1535, or TA1537 (Mortelmans *et al.* 1986). It did not cause gene mutations in *Drosophila melanogaster* (Fourman *et al.* 1994). In mammalian *in vitro* systems, it caused gene mutations in mouse lymphoma cells (McGregor *et al.* 1988), DNA damage in Chinese hamster ovary (CHO) cells (NTP 1993), and chromosomal damage in CHO cells with mammalian metabolic activation (NTP 1993, IARC 1995), but it did not cause DNA damage in mouse or rat hepatocytes (Wilson *et al.* 1992, NTP 1993). In mammalian *in vivo* systems, furan caused chromosomal aberrations in bone marrow of mice (NTP 1993, Johansson 1997), but did not cause DNA damage in mouse bone marrow or hepatocytes or rat hepatocytes (Wilson *et al.* 1992, NTP 1993).

A current hypothesis for the mechanism of furan-induced carcinogenesis is metabolic activation of furan by cytochrome P450 to a reactive and cytotoxic intermediate that stimulates cell replication, increasing the likelihood of tumor induction (Kedderis *et al.* 1993, Chen *et al.* 1995). The postulated reactive metabolite is *cis*-2-butene-1,4-dial, which was characterized as a furan metabolite by Chen *et al.* (1995). This reactive metabolite probably explains furan's binding reactivity with proteins both *in vitro* (in uninduced and induced male rat liver microsomes) and *in vivo* (with male rat liver protein) (Burka *et al.* 1991, Parmar and Burka 1993). Furan metabolites may react with DNA, but no radiotracer was detected in DNA from livers of rats administered [¹⁴C]furan (Burka *et al.* 1991).

Properties

Furan is a cyclic dienic ether that is a clear, colorless liquid with an ethereal odor (Akron 2009, HSDB 2009). It can turn brown upon standing (HSDB 2009). Furan is slightly soluble in water and is soluble at greater than 10% in acetone, benzene, ether, and ethanol. It is extremely flammable and may form explosive peroxides in the absence of inhibitors (Akron 2009). Physical and chemical properties of furan are listed in the following table.

Property	Information
Molecular weight	68.1 ^a
Specific gravity	0.9371 at 19.4°C/4°C ^a
Melting point	-85.6°C ^a
Boiling point	31.4°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	1.34 ^a
Water solubility	10 g/L at 25°C ^b
Vapor pressure	600 mm Hg at 25°C ^b
Vapor density relative to air	2.3 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Furan is used primarily as an intermediate in the synthesis and production of tetrahydrofuran, pyrrole, and thiophene. Hydrogenation of furan over a nickel catalyst produces high yields of tetrahydrofuran and is a source of commercial tetrahydrofuran (NTP 1993, IARC

1995). Furan is also used in the formation of lacquers, as a solvent for resins, and in the production of agricultural chemicals, stabilizers, and pharmaceuticals (IARC 1995, HSDB 2009).

Production

Commercial production of furan involves decarbonylation of furfural over a palladium-charcoal catalyst. The commercial product is at least 99% pure (IARC 1995). In 2009, furan was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 20 suppliers, including 11 U.S. suppliers (ChemSources 2009). U.S. imports of furan resins totaled about 9.7 million pounds in 1986 (HSDB 2009). Reports filed from 1986 to 1998 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of furan totaled 10 million to 50 million pounds (EPA 2004); no reports were filed in 2002.

Exposure

The routes of potential human exposure to furan are inhalation, ingestion, and dermal contact. The pattern of commercial use suggests that minimal exposure to the general population would be expected through contact with products contaminated with furan (NTP 1993). However, furan can be formed in foods during processing. Furan has been detected in the breath of both smokers and nonsmokers and in indoor air, foods, and human milk samples (IARC 1995, NTP 1999, FDA 2005). Furan also occurs naturally in pine rosin and in volatile emissions from sorb trees (HSDB 2009).

Furan was measured by the U.S. Food and Drug Administration in various foods and beverages, including infant formulas, baby foods, soups and sauces, fruits and vegetables, bread, and meat products. The maximum concentration found was 125 ppb ($\mu\text{g}/\text{kg}$) in canned soup (FDA 2005). A second study confirmed that heat-treated foods, such as canned and jarred foods, contained measurable quantities of furan (up to 240 $\mu\text{g}/\text{kg}$ in canned chili) (Becalski *et al.* 2005). Furan was measured in fruit juice at concentrations near 1 $\mu\text{g}/\text{kg}$ (Goldmann *et al.* 2005). In several brands of brewed coffee, the highest furan concentration found was 84.2 ppb (FDA 2005, Ho *et al.* 2005). Furan was also identified as a component of coffee aroma that has antioxidant activity (Fuster *et al.* 2000). Furan was also detected at a concentration of 110 $\mu\text{g}/\text{kg}$ in jarred baby food containing cooked vegetables (Goldmann *et al.* 2005). However, furan concentrations decreased after the jar was opened and the contents were heated. When food is heated in a container, furan concentrations increase if the container remains closed, but not if it is open (Hasnip *et al.* 2006). Furan does not appear to be transferred from the packaging or gasket of the can or jar. Furan is formed from ascorbic acid, fructose, sucrose, and glucose when foods are heated or irradiated (Fan 2005). Furan production increases greatly with decreasing pH of the medium; 1,600 times as much furan is formed at pH 3 as is formed at pH 8. Furan was detected in 1 of 11 breast-milk samples from women in four different urban areas (HSDB 2009).

In one study in Texas, furan was detected in the exhaled breath of two of three male smokers and four of five male nonsmokers (HSDB 2009). Smokers exhaled between 0.25 and 98 μg of furan per hour, and nonsmokers exhaled between 0.33 and 28 $\mu\text{g}/\text{h}$. In a study in Chicago, 15 of 387 breath samples collected from 54 male and female nonsmokers had detectable levels of furan, with a mean concentration of 0.55 ng/L. Furan was also detected in the indoor air of homes in the Chicago, Illinois, and Washington, D.C., metropolitan areas (NTP 1999).

If furan is released to air, it will exist almost entirely in the vapor phase (Howard 1989). In daylight, it will react with hydroxyl radicals,

with a half-life of 9.5 hours. Furan is resistant to hydrolysis. Its estimated half-life in a shallow model river is 2.5 hours. If released to surface water, it will volatilize rapidly and will not adsorb to sediment or suspended solids or bioaccumulate in aquatic organisms. If released to soil, it will volatilize or leach rapidly. Furan has been detected in industrial effluents, ambient air, wood smoke, and automobile exhaust and in surface water. However, the frequency of detection and concentration generally were low. For example, furan was detected in 1 of 63 industrial effluents at concentrations of less than 10 $\mu\text{g}/\text{L}$ and in aqueous condensate samples from low-temperature gasification of rosebud coal at 7 $\mu\text{g}/\text{L}$ (IARC 1995, HSDB 2009).

The primary route of occupational exposure to furan is inhalation. The industrial processes in which furan is used are conducted in closed systems, and its volatility requires that furan be handled in closed containers; therefore, occupational exposure is limited (NTP 1993). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 244 workers potentially were exposed to furan (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 35 workers (mostly in the Business Services industry), including 7 women, potentially were exposed to furan (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Furan is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Prevention of Accidental Release: Threshold quantity (TQ) = 5,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 500 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of furan = U124.

Occupational Safety and Health Administration (OSHA)

Considered a highly hazardous chemical; threshold quantity (TQ) = 500 lb.

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Certain Glass Wool Fibers (Inhalable)

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994) as Glass Wool (Respirable Size)

Carcinogenicity

Certain glass wool fibers (inhalable) are *reasonably anticipated to be human carcinogens* based on (1) sufficient evidence of carcinogenicity from studies in experimental animals of inhalable glass wool fibers as a class (defined below) and (2) evidence from studies of fiber properties which indicates that only certain fibers within this class — specifically, fibers that are biopersistent in the lung or tracheo-bronchial region — are *reasonably anticipated to be human carcinogens*. Because there is considerable variation in the physicochemical and biophysical properties of individual glass wool fibers, carcinogenic potential must be assessed on a case-by-case basis in experi-

mental animals, through either long-term carcinogenicity assays or assays measuring the persistence of fibers in the lung. Regulatory authorities in Germany and the European Union have developed testing protocols and criteria for categorizing fibers with respect to their carcinogenicity that do not require long-term carcinogenicity studies in animals; however, the criteria used by these two groups differ somewhat. Studies on mechanisms of carcinogenesis provide additional support for the findings of studies in experimental animals that certain (inhalable) glass wool fibers are carcinogenic; however, the available studies in humans are inadequate to evaluate the potential carcinogenicity of glass wool fibers.

The class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 µm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breyse *et al.* 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, “inhalable” fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheo-bronchial tree (Quinn *et al.* 1997, Husain 2010).

“Glass Wool (Respirable Size)” was first listed in the *Seventh Annual Report on Carcinogens* as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals. “Respirable” fibers are those that can penetrate into the alveolar region of the lung upon inhalation (EPA 2001) (see Properties for a more detailed description). Since that time, additional studies have been conducted to evaluate the physicochemical properties of glass wool fibers related to carcinogenicity. The listing was changed in the *Twelfth Report on Carcinogens* to “Certain Glass Wool Fibers (Inhalable),” which are listed as *reasonably anticipated to be human carcinogens*.

Cancer Studies in Experimental Animals

Glass wool fibers caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Individual types of glass wool fibers were studied in chronic carcinogenicity bioassays in rats and/or hamsters exposed by a number of routes, including inhalation, intratracheal instillation of fiber suspensions, surgical intrathoracic implantation, and direct exposure to the pleural or peritoneal cavity by injection. The studies employed various glass wool products and treated or sized fractions of the products. Inhalation exposure studies used respirable fibers as defined by World Health Organization criteria (see Properties) unless otherwise specified.

The most biologically relevant studies were of inhalation exposure to respirable or inhalable fibers in rats and hamsters. These studies used the exposure route and fiber dimensions most relevant to human exposure conditions. Although intratracheal instillation (a bolus injection into the trachea) bypasses the upper respiratory airway, exposure by this route also is relevant to human exposure. Both intratracheal and inhalation exposure conditions target the lung and pulmonary clearance mechanisms within that environment. Intra-

thoracic, intrapleural, and intraperitoneal exposures are less relevant biologically, as they target the mesothelial lining of the pleural and peritoneal cavities; however, studies using these routes do provide information about fiber biodurability (resistance to dissolution or disintegration in the body) and cancer hazard. Studies of the carcinogenicity of glass wool fibers following chronic exposure, described below, are organized by fiber use (special purpose, insulation, unspecified, or experimental) and route of exposure.

Special-Purpose Glass Fibers

The majority of studies that found carcinogenic effects of glass wool fibers tested special-purpose fibers. Most of the studies used type 475 glass fibers; one study tested E-glass fibers; and one tested a series of unspecified special-purpose fibers. Type 475 glass fibers are coded according to mean fiber diameter, with larger numbers indicating larger diameters (e.g., Johns Manville [JM] 110/475 fibers have a greater nominal diameter [1.9 to 3.0 μm] than JM 100/475 fibers [0.28 to 0.38 μm]). Man-made vitreous fiber (MMVF) 33 is a mixture of respirable fibers of type 475 glass codes 104, 108B, and 110.

Inhalation Exposure

Inhalation exposure to E-glass fibers significantly increased the incidences of lung cancer (carcinoma) and total lung tumors (carcinoma and adenoma) in male Wistar rats; mesothelioma was observed in two animals (Cullen *et al.* 2000).

Inhalation exposure to MMVF 33 glass fibers caused a single mesothelioma in a male Syrian golden hamster, but no lung tumors. Although the incidence of mesothelioma was not significantly increased, the mesothelioma was believed to be exposure-related because of (1) the high incidence of fibrosis, mesothelial hypertrophy, and mesothelial hyperplasia of the pleura in exposed hamsters, (2) the rarity of the spontaneous occurrence of this type of tumor, and (3) the presence of glass fibers in the thoracic wall and diaphragm (Hesterberg *et al.* 1997, McConnell *et al.* 1999).

Inhalation exposure of F344 rats to two different glass fibers — (1) Tempstran code 100/475 glass fibers without binder in two sizes (average diameter < 3.5 μm , length either < 10 μm or > 10 μm) and (2) Owens-Corning FM series air-filter media with binder (average diameter 0.5 to 3.5 μm , length > 10 μm) — significantly increased the incidence of mononuclear-cell leukemia in rats (males and females combined) (chi-square test and one-tailed Fisher's exact test). The incidence of mononuclear-cell leukemia also exceeded the range of the historical control values for the testing laboratory. Although F344 rats have a high spontaneous incidence of mononuclear-cell leukemia, these findings were considered to be exposure-related because of the presence of granulomatous pleural and subpleural plaques and glass-laden macrophages in adjoining lymph nodes. Glass-fiber-related pulmonary and tracheal-bronchial lymph-node lesions were more severe following exposure to the shorter Tempstran 100/475 fibers than to the other fibers tested (Mitchell *et al.* 1986, Moorman *et al.* 1988).

Other Routes of Exposure

Intratracheal instillation of JM 104/475 glass fibers significantly increased the incidences of lung tumors (adenoma, adenocarcinoma, and squamous-cell carcinoma) in female Wistar rats (Pott *et al.* 1987) and thoracic tumors (carcinoma of the lung, mesothelioma, and thoracic sarcoma) in one of two studies in male Syrian hamsters (Pott *et al.* 1984, Feron *et al.* 1985). In female Osborne-Mendel rats administered 11 types of unspecified special-purpose glass fibers by intrathoracic implantation, the incidence of mesothelioma was significantly increased for 7 of the types of glass fiber (compared with the incidence in a control group implanted with autoclaved gelatin-

saturated coarse fibrous glass vehicle comparable in weight to the test fibers plus vehicle) (Stanton *et al.* 1977, 1981). Intrapleural or intratracheal injection of type 475 glass fibers (codes 100, 104, or 110) caused mesothelioma in rats (Sprague-Dawley, Wistar, or Osborne-Mendel) (Wagner *et al.* 1976, 1984, Monchaux *et al.* 1981, Pott *et al.* 1987, Smith *et al.* 1987). Sarcoma and unspecified tumors also were observed in rats administered type 475 glass fibers by intraperitoneal injection (Pott *et al.* 1984, Muhle *et al.* 1987, Miller *et al.* 1999).

Insulation Glass Fibers

Types of insulation glass wool fibers tested in experimental animals included Owens-Corning glass wool, MMVF 10 and 10a (both of which represent the respirable fraction of Manville 901 glass fiber), MMVF 11 (the respirable fraction of CertainTeed B glass fiber), and unspecified glass wool fibers. Inhalation exposure of F344 rats to Owens-Corning FG insulation fiberglass with binder (4 to 6 μm in diameter and > 20 μm long) significantly increased the incidence of mononuclear-cell leukemia in rats (males and females combined). Glass-fiber-related pulmonary and tracheal-bronchial lymph-node lesions were observed but were less severe than for exposure to special-purpose fibers. As with the findings for Tempstran 100/475 glass fibers in this strain (discussed above), these findings were considered to be exposure-related (Mitchell *et al.* 1986, Moorman *et al.* 1988). Intraperitoneal injection of MMVF 11 glass fibers caused mesothelioma of the abdominal cavity in male and female Wistar rats (Roller *et al.* 1996, 1997), and intraperitoneal injection of MMVF 10 glass fibers increased tumor rates in male Wistar rats (Miller *et al.* 1999).

Fibers with Unspecified Commercial Applications

For Schleicher and Schuell (S&S 106) glass wool fibers, information on commercial applications is not clear. Intraperitoneal injection of S&S 106 glass fibers in female Wistar rats caused dose-dependent increases in the incidences of mesothelioma and combined tumors (mesothelioma and spindle-cell sarcoma) (Pott 1976).

Experimental Fibers

Male and female Wistar rats injected intraperitoneally with B-1, B-09, or B-20 glass fibers developed mesothelioma of the abdominal cavity (Roller *et al.* 1996, 1997), which was also observed at a low incidence in female Wistar rats injected with the biosoluble glass wool fibers B, P, and V (Grimm *et al.* 2002).

Summary

A range of carcinogenic responses was observed in experimental animal studies; for example, some glass wool fibers were carcinogenic by several routes of exposure, including inhalation; some were carcinogenic only by routes of exposure other than inhalation; and some were not carcinogenic in any studies. Studies in experimental animals demonstrate a greater carcinogenic effect for special-purpose fibers than for insulation wool. In general, special-purpose fibers are more durable than insulation glass wool fibers; these findings thus suggest that durability is an important factor in predicting the potential carcinogenicity of glass wool fibers. The available studies in experimental animals clearly demonstrate that glass wool fibers are carcinogenic; however, their utility for predicting the carcinogenicity of specific fibers or groups of fibers is limited, for several reasons: (1) Only a subset of commercially available fibers have been tested. (2) Commercial applications and specific products may change over time; the specific fibers tested may no longer represent the products to which individuals are exposed. (3) The physicochemical properties of glass wool vary within each category. (4) The sizes of fibers used in various applications overlap, and each specific product con-

tains fibers with a wide range of diameters (see Properties for a discussion of nominal diameter in glass wool products). (5) Testing of some specific fibers was limited. In general, more studies were conducted with special-purpose fibers than insulation fibers. Some fibers, such as 475 glass fibers, were tested under several different sets of experimental conditions by several investigators, whereas other fibers, such as FG insulation fiberglass, were tested in only one study. Advances have been made in the study of fiber properties related to carcinogenicity; as discussed below, mechanistic and biologically based modeling studies of synthetic vitreous fibers (which include glass wool fibers) suggest that fiber shape and biodurability are important determinants of carcinogenicity.

Fiber Properties Related to Carcinogenicity

The potential for exposure to glass wool fibers to cause cancer is influenced by dose, fiber dimensions (length and diameter), and durability. Inhalation exposure studies showed that tumor incidence or lesion severity increased with the concentration of fibers in the lung (Bunn *et al.* 1993, McConnell 1994, Hesterberg *et al.* 1999, McConnell *et al.* 1999). The cumulative lung burden of fibers is related to their deposition and their biopersistence, which is the ability of fibers to remain in the lung. Fiber aerodynamic diameter (see Properties) determines whether a fiber will be deposited in the lungs or the upper airways; thinner fibers will be deposited into the deep lung (Hesterberg and Hart 2001). Because most human lung cancer occurs within the first five generations of the tracheobronchial tree, it is important to consider both inhalable and respirable fibers (Quinn *et al.* 1997). Fiber length can also influence fiber deposition; the deposition fraction for fibers 1 μm in diameter and 20 μm long is fivefold higher in the tracheobronchial region than in the pulmonary region (Muhle and Bellmann 1997). Biopersistence depends on the fiber's biodurability and its physiological clearance by the lung. Fiber size and durability are important determinants of biopersistence (Hesterberg and Hart 2001). Biodurability is determined by fiber dimensions (length and width) and chemical composition (Muhle and Bellmann 1997). Fiber length also affects whether fibers are cleared from the lung; in rats, fibers shorter than 10 μm presumably are phagocytized by alveolar macrophages, but longer fibers cannot be cleared until they dissolve or break into shorter fragments. Macrophage-mediated clearance of insoluble particles is significantly faster in rats than in humans. Long, durable fibers can persist in the lung for extended periods, and the more biopersistent the fiber, the greater its potential to exert biological effects on the lung (Hesterberg and Hart 2001, Bellmann *et al.* 2010).

Bernstein *et al.* (2001a,b) reported that "biopersistence clearance half-time" was a good predictor of both the collagen deposition (fibrosis) observed in chronic inhalation and intratracheal instillation studies and the tumor response observed in intraperitoneal injection studies. The inhalation half-times for fibers over 20 μm long were found to correlate with the number of fibers remaining after chronic inhalation exposure. The average collagen score after chronic inhalation exposure correlated with intratracheal instillation half-times for fibers over 20 μm long and for respirable fibers as defined by the World Health Organization ("WHO fibers": diameter < 3 μm , length \geq 5 μm , and aspect ratio \geq 3:1). Exposure to fibers with a weighted half-time of less than 40 days by intratracheal instillation or less than 10 days by inhalation exposure resulted in a baseline level of collagen deposits (a precursor of interstitial fibrosis) at the bronchioalveolar junction. Furthermore, the biopersistence half-times of fibers as determined for inhalation (weighted half-time of fibers > 20 μm) and intratracheal instillation (weighted half-time of fibers > 20 μm and half-time of WHO fibers) were predictive of the tumor response in

long-term intraperitoneal-injection studies (Bernstein *et al.* 2001b). The short-term biopersistence test is used by both the European Union and Germany to classify the carcinogenicity of synthetic vitreous fibers. Both the European Union and Germany classify synthetic vitreous fibers as possibly or probably carcinogenic, but fibers are exempted from classification if they meet testing criteria for exoneration based on a cancer bioassay or a short-term biopersistence test. The European Union's criteria for exoneration are based on both inhalation and intraperitoneal exposure (in either a cancer bioassay or the short-term biopersistence test), whereas the German criteria are based only on intraperitoneal exposure; the Germans have questioned the sensitivity of the inhalation carcinogenicity assays for fibers in rats (Collier 1995, Wardenbach *et al.* 2005). The German criteria use the half-time of fibers over 5 μm long, whereas the European Union criteria use the weighted half-time of fibers over 20 μm long (Bernstein 2007).

Numerous studies have evaluated the relationship between fiber shape or fiber solubility and tumor incidences, and have attempted to define quantitative values for size and durability that are correlated with tumor incidence or that predict carcinogenicity. Studies investigating synthetic vitreous fiber properties and carcinogenicity demonstrated a relationship between fiber size or shape and tumor incidence or biological activity of fibers related to carcinogenicity (Stanton *et al.* 1977, 1981; Quinn *et al.* 2000). Longer, thinner fibers are carcinogenic; however, the specific fiber dimensions considered to be carcinogenic varied among studies, and the critical length of fibers with respect to carcinogenicity is not clear (Bellmann *et al.* 2010).

As noted above, fiber dissolution is an important determinant of lung clearance. Various investigators have evaluated *in vitro* simulation of fiber dissolution to predict biological durability in the extracellular media. A mathematical model relating the *in vitro* dissolution constant (K_{dis}) to fiber carcinogenicity and fibrosis provided evidence that K_{dis} values at pH 7.4 could be used to predict tumorigenicity for inhalation exposure (Eastes and Hadley 1996). Long fibers (> 20 μm) were considered in this model, as these fibers cannot be rapidly cleared from the lung by macrophages, so their persistence in the lung is related to physical properties of the fiber, such as solubility. The model predicted that a fiber with a dissolution rate of 100 ng/cm² per hour or greater has an insignificant chance of producing fibrosis or tumors in rats exposed by inhalation. Although *in vitro* testing is useful for designing soluble fibers, limitations for predicting lung tumorigenicity using K_{dis} have been reported (Bauer *et al.* 1994, Muhle *et al.* 1994, Zoitos *et al.* 1997, Guldberg *et al.* 1998, Bellmann *et al.* 2010). As of 2010, no regulatory agency in the United States or the European Union had adopted the dissolution constant as a predictor of fiber carcinogenicity.

Studies on Mechanisms of Carcinogenesis

Fiber properties such as dimensions, chemical composition, and surface reactivity and the dose of fibers determine whether a fiber can be effectively engulfed by an alveolar macrophage and efficiently cleared from the lungs or remain and cause a chronic inflammatory response (Nguea *et al.* 2008). If fibers are too long for the macrophage to effectively engulf or are too durable to break or dissolve within the lung or macrophage environment, incomplete phagocytosis can result in excessive production of reactive oxygen species (ROS) and inflammatory mediators and their release into the lung, which can lead to chronic inflammation and fibrosis (Hesterberg and Hart 2001). Fibers not cleared by macrophages can also be taken up by lung epithelial cells and translocated to the pleural space, resulting in chronic inflammation, tissue damage, cell proliferation, and fibrosis (Oberdörster 2002). Chronic inflammation, fibrosis, and fi-

brotic nodules have been found to be associated with mesothelioma formation after intracavity injection of glass wool fibers, suggesting that oxidative stress from inflammation has a role in mesothelioma formation (Grimm *et al.* 2002). An increase in oxidative stress but no increase in mutation frequency was observed in the lungs of rats following intratracheal exposure to glass wool (Topinka *et al.* 2006). Culturing primary rat alveolar cells with glass fibers induced a pro-inflammatory cytokine, tumor necrosis factor- α , through activation of both mitogen-activated protein (MAP) kinase and nuclear factor- κ B (NF- κ B) gene transcription pathways (Ye *et al.* 1999, 2001). MAP kinase and NF- κ B are important factors in cell-signaling pathways controlling cell proliferation and cell death, and they can be activated by ROS. In these studies, long fibers ($16.7 \pm 10.6 \mu\text{m}$) were more potent than short fibers ($6.5 \pm 2.7 \mu\text{m}$) in activating MAP kinases.

Glass wool fibers have the potential to cause genetic damage (Nguea *et al.* 2008). *In vitro*, they caused production of ROS in cell-free systems and oxidative damage in cell-culture systems. In cultured mammalian cells, they caused DNA damage, micronucleus formation, chromosomal aberrations, and DNA-DNA interstrand cross-links (NTP 2009). Intratracheal instillation of insulation glass wool caused DNA strand breaks in rat alveolar macrophages and lung epithelial cells. Although fibers of various dimensions caused DNA damage in mammalian cells, longer fibers were more potent in causing these genotoxic effects (Topinka *et al.* 2006).

In cytotoxicity studies, longer fibers were more toxic than shorter fibers to rat alveolar macrophages (Hart *et al.* 1994, Blake *et al.* 1998). Exposure to glass wool fibers in a cell transformation assay caused cytotoxicity and anchorage-independent growth in mouse fibroblasts; amplification of the proto-oncogenes *K-ras*, *H-ras*, *c-fos*, and *c-myc*; and mutations in *K-ras* and *p53* tumor-suppressor genes (Gao *et al.* 1995, Whong *et al.* 1999). Exposure to glass wool fibers also caused cytotoxicity and morphological transformation in Syrian hamster embryo cell cultures (Hesterberg and Barrett 1984). Thick fibers (average diameter = $0.8 \mu\text{m}$, average length = $9.5 \mu\text{m}$) were 20-fold less potent than thin fibers of the same length (average diameter = $0.13 \mu\text{m}$) in causing cell transformation, and shorter fibers (average length = $1.7 \mu\text{m}$, average diameter = $0.13 \mu\text{m}$) were 10-fold less potent than longer fibers of the same diameter (average length = $9.5 \mu\text{m}$). Cytotoxic potencies of the fibers were associated with their transforming potencies. These results provide evidence that fibers can have direct cytotoxic and transforming effects on cells, and that the magnitude of the response is related to fiber dimensions.

Cancer Studies in Humans

The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure to glass wool fibers. Although studies of occupational exposure found excess lung-cancer mortality or incidence, it is unclear that the excess lung cancer was due to exposure specifically to glass wool fibers, because (1) no clear positive exposure-response relationships were observed (however, misclassification of exposure is a concern), and (2) the magnitudes of the risk estimates were small enough to potentially be explained by co-exposure to tobacco smoking.

The data relevant for evaluation of exposure specifically to glass wool fibers are from studies of four major cohorts of glass wool manufacturing workers in the United States (Marsh *et al.* 2001a,b, Youk *et al.* 2001, Stone *et al.* 2001, 2004), Europe (Boffetta *et al.* 1997, 1999), Canada (Shannon *et al.* 2005), and France (Moulin *et al.* 1986) and a hospital-based case-control study of lung cancer among Russian workers exposed to glass wool (Baccarelli *et al.* 2006). The most informative studies are the U.S. multi-plant cohort study and a nested case-control study of lung cancer within that cohort, because they

(1) had adequate statistical power to detect an effect, because of the cohort's large size ($> 10,000$ male and female workers) and long follow-up period, (2) adjusted for tobacco smoking (in the nested case-control study of male workers), (3) used internal analyses to evaluate quantitative exposure to respirable fibers (using non-exposed workers in the cohort as the reference group), and (4) separated the results for women (the only studies to do so). The French study was the least informative, because of its short follow-up period. The U.S. study reported mortality data, the French study reported incidence data, and the European and Canadian studies reported both mortality and incidence data. Respiratory cancer (including upper-respiratory-tract and lung cancer) and mesothelioma were the cancers of interest; the data were inadequate to evaluate cancer at other tissue sites. None of the studies clearly distinguished between exposure to glass wool used for insulation or for special-purpose applications.

Respiratory-System or Lung Cancer

Excesses of respiratory cancer mortality or incidence were found in three of the four cohort studies (not adjusted for smoking) and the case-control study of Russian workers (adjusted for smoking); the fourth (French) cohort had limited statistical power to detect an effect because of the very small number (5) of cases among exposed workers. Findings were statistically significant in the U.S. study (standardized mortality ratio [SMR] = 1.18, 95% confidence interval [CI] = 1.04 to 1.34, 243 exposed deaths, males and females, specific for glass wool plants) and the Canadian study (SMR = 1.63, 95% CI = 1.18 to 2.21, 42 exposed deaths; standardized incidence ratio [SIR] = 1.60, 95% CI = 1.19 to 2.11, 50 exposed cases). A meta-analysis of the four cohorts yielded a summary relative risk (RR) that approached statistical significance (RR = 1.22, 95% CI = 1.00 to 1.49, 920 exposed cases) (Lipworth *et al.* 2009). (The meta-analysis used risk estimates for workers at both filament and glass wool plants in the U.S. study and mortality data for the Canadian and European cohorts.)

The association between cancer and exposure to glass wool fibers among men and women in the U.S. cohort was evaluated by internal analyses, using unexposed workers as the reference group for men and workers exposed to filament fibers for women. The nested case-control study of lung cancer among male workers found no evidence of an association between working in plants manufacturing glass wool fibers and respiratory system cancer (lung, larynx, trachea, or bronchus) after adjusting for tobacco smoking (RR = 1.06, 95% CI = 0.71 to 1.6). In exposure-response analyses, no association was found between cumulative exposure or average intensity or duration of exposure to respirable glass fibers (Marsh *et al.* 2001b, Stone *et al.* 2001, Youk *et al.* 2001). However, exposure misclassification is a concern. Quinn *et al.* (1996, 1997, 2000, 2005) suggested that the indices of exposure (NIOSH Method 7400 B; see Exposure, below) used in these studies may not reflect the fiber characteristics most related to development of cancer, which could result in a considerable loss of power to detect exposure effects.

In contrast to the findings for male workers, there was some evidence for an increased risk of respiratory-system cancer among female workers in glass wool plants (unadjusted RR = 3.24, 95% CI = 1.27 to 8.28), based on 6 cases in exposed workers (Stone *et al.* 2004). Employment duration and time since first employment were significantly related to respiratory-cancer mortality, but no association was found with cumulative exposure to respirable fibers. Estimates were not adjusted for smoking, but a survey of smoking habits among a subset of workers found a slightly lower (24.5%) percentage of current smokers among workers than in the general population (29%). The meaning of the finding of a potential association with lung-cancer

mortality among women, but not men, is unclear, because women had lower exposure than men.

The Russian hospital-based case-control study found higher risk estimates for workers exposed at higher levels, but no trends were found for cumulative exposure (Baccarelli *et al.* 2006). Although the Canadian and European studies did not evaluate quantitative exposure to glass wool fibers, they did evaluate risk by employment duration and latency. No clear exposure-response patterns for lung cancer mortality were observed in either study, although an approximately threefold increase in mortality was observed among Canadian workers with over 20 years of employment duration and over 40 years since first exposure (Shannon *et al.* 2005).

Cancer of the Upper Respiratory and Alimentary Tracts

Excesses in the incidence of cancer of the upper respiratory tract and alimentary tract (oral cavity, pharynx, and larynx) were reported for the European cohort (SIR = 1.41, 95% CI = 0.80 to 2.28, 16 exposed cases) and French cohort (SIR = 2.18, 95% CI = 1.31 to 3.41, 19 exposed cases); risks increased with increasing exposure duration in the French cohort (Moulin *et al.* 1986) and time since first employment in the European cohort ($P_{\text{trend}} = 0.03$). Findings for these combined tissue sites were not reported in the Canadian study. Excess mortality from buccal and pharyngeal cancer also was observed in the European study, but was not related to time since first employment or employment duration; no excess of buccal and pharyngeal cancer was observed in the U.S. study. A meta-analysis using mortality data from the U.S. study (not including laryngeal cancer) and incidence data from the European study (not including laryngeal cancer) and the French study found an elevated but statistically nonsignificant risk for head and neck cancer (summary RR = 1.42, 95% CI = 0.91 to 2.1). The interpretation of these findings is unclear, because of limited exposure-response analyses and lack of adjustment for tobacco smoking (Lipworth *et al.* 2009).

Mesothelioma

The available data are inadequate to evaluate the association between glass wool exposure and mesothelioma, a rare cancer strongly linked to asbestos exposure. Mesothelioma was evaluated in detail only for the U.S. cohort; in the other studies, the reporting on mesothelioma either was not specific for exposure to glass wool fibers (Engholm *et al.* 1987, Rodelsperger *et al.* 2001) or did not evaluate co-exposure to asbestos (Boffetta *et al.* 1997). In the U.S. cohort, two cases of mesothelioma were identified among workers with exposure to glass wool but without known exposure to asbestos; in one case, there was uncertainty in the cancer diagnosis, and in the other case, information on asbestos exposure was not complete (Marsh *et al.* 2001a).

Properties

Glass wools fibers are a subcategory of synthetic vitreous fibers, which are manufactured inorganic fibrous materials that contain aluminum or calcium silicates and are made from a variety of materials, including rock, clay, slag, or glass (ATSDR 2004). The chemical composition of glass wool products varies depending on the manufacturing requirement and end use, but almost all contain silicon dioxide as the single largest oxide ingredient for the production of glass (IARC 2002). Silicon dioxide or one of a few other oxides (boron trioxide, phosphorus pentoxide, or germanium dioxide) is required in order to form glass, and these oxides are known as "glass formers." The essential property of a glass former is that it can be melted and quenched into the glassy (amorphous) state. Commercial glasses generally include additional oxides that serve as stabilizers and modifiers or fluxes; they modify the physical and chemical properties of the glass prod-

uct, including viscosity (NTP 2009). These modifiers include oxides of aluminum, titanium, zinc, magnesium, lithium, barium, calcium, sodium, and potassium.

Glass wool products consist of individual fibers, which have been basically defined since the late 1950s as being over 5 μm long and having an aspect ratio of at least 3:1 (Walton 1982, Breyse *et al.* 1999). Other, more recent, definitions have suggested that an aspect ratio of 5:1 will more readily discriminate fibrous from irregularly shaped particles, and some organizations have adopted this criterion. In addition to differences in the chemical composition of the glass used to make the fibers, the fibers themselves can be modified further by addition of various lubricants, binders, antistatic agents, extenders and stabilizers, and antimicrobial agents.

The primary physical characteristics of glass wool fibers are their diameter and length. The fiber diameter is controlled by the manufacturing process. All glass fibers are manufactured to nominal diameters that vary based on the manufacturing process and the fibers' intended use (ACGIH 2001). The nominal diameter is an estimate of the product's average fiber diameter. Because current glass wool production processes are not capable of producing fibers only at the nominal diameter, the diameters of individual fibers in a glass wool product vary widely around the nominal diameter (IARC 2002). Insulation glass fibers typically have nominal diameters of 1 to 10 μm , and special-purpose fibers have nominal diameters of 0.1 to 3 μm ; however, a product with an average diameter of 5 μm can contain fibers with diameters ranging from less than 1 to over 20 μm (ACGIH 2001, IARC 2002).

The manufacturing process also affects fiber length. In glass wool insulation, most fibers are several centimeters long; however, fibers break crosswise, and lengths of less than 250 μm (considered to be the upper limit of respirability) probably are present in all glass wool products (IARC 2002). Respirable fibers are defined as those that can penetrate into the alveolar region of the lung upon inhalation; in humans, a fiber with an aerodynamic diameter of less than 5 μm is respirable (EPA 2001). Aerodynamic diameter, unlike geometric diameter, takes into account fiber density and aspect ratio. The World Health Organization defines respirable fibers as those with an aerodynamic diameter of less than 3 μm , a length of greater than 5 μm , and an aspect ratio of at least 3:1 (WHO 2000). In this profile, "inhalable" fibers include all fibers that can enter the respiratory tract, including respirable fibers; fiber sizes are given as geometric diameter and length except as noted.

Use

Glass fibers can generally be classified into two categories based on usage: (1) low-cost, general-purpose fibers typically used for insulation applications and (2) premium special-purpose fibers used in limited specialized applications. The primary use of glass wool is for thermal and sound insulation. The largest use of glass wool is for home and building insulation in the form of loose wool, batts (insulation in the form of a blanket, rather than a loose filling), blankets or rolls, or rigid boards for acoustic insulation. Glass wool is also used for industrial, equipment, and appliance insulation.

Special-purpose glass fibers are used for a variety of applications that require either a specialized glass formulation or a particular diameter. The largest market for special-purpose glass fibers is for battery separator media; the glass wool fibers physically separate the negative and positive plates in a battery while allowing the acid electrolyte to pass through. Another important use is in high-efficiency particulate air filters for settings where high-purity air is required. Special-purpose glass fibers are also used for aircraft, spacecraft, and acoustical insulation.

Production

Manufacture of glass wool consists of three main steps: mixing the raw materials and melting them to form glass; forming fibers (i.e., fiberizing); and finishing the products (Quinn *et al.* 2001, Smith *et al.* 2001, IARC 2002, NTP 2009). Fibers are formed when molten glass at approximately 1,370°C (2,500°F) is either forced through mechanical spinners by centrifugal force (rotary process) and separated with a blast of air or when molten glass filaments are attenuated by steam (steam blowing) or a circular burner flame (flame attenuation) and forced air that breaks the fibers into shorter lengths. The ranges of nominal diameter produced are 5 to 12 µm by steam blowing; less than 2, 2 to 4, or 4 to 8 µm by rotary blowing; and less than 2 or 2 to 4 µm by flame attenuation. If the purpose of the fibers is production of home and building insulation products, the newly formed fibers are usually sprayed with a binder, typically phenol-formaldehyde. The finishing process begins with collection of the fibers within the forming chamber to create a mat on a suction conveyor belt of porous metal in a hood. The fiber mat with binder exits the forming hood via the conveyor carrier through a gas-fired oven, which cures the binder. Final processing consists of cutting the mat into batts, rolls, or other shapes. Uncoated fibers are simply bagged.

In 2000, an estimated 3,388 million pounds (1.7 million tons) of fiberglass were used in building insulation, about 81% in residential construction and 19% in commercial or industrial construction (Maxim *et al.* 2003). The Glass Manufacturing Industry Council reported that in 2002, 10 major manufacturers operated about 40 U.S. plants producing about 3 million tons of all types of glass fiber, including glass wool (ATSDR 2004). Special-purpose glass fibers, produced by at least four U.S. companies, account for only about 1% of total annual U.S. production of synthetic vitreous fiber (Carey 2004).

The United States International Trade Commission reports U.S. imports and exports of glass fibers only by dollar value. Imports are reported in five product categories: (1) mats, nonwoven, of glass fibers, (2) thin sheets (voiles), nonwoven, of glass fibers, (3) batts of nonwoven glass fibers, (4) pipe coverings of nonwoven glass fibers, and (5) other insulation products of nonwoven glass fibers. The combined value of imports in these categories varied considerably between 2000 and 2008, from a low of \$189 million in 2001 to a high of \$356 million in 2006; the value for 2008 was \$196 million (USITC 2009a). The value of U.S. exports in the product category “insulation products of glass fibers” increased steadily from \$59 million in 2000 to \$121 million in 2008 (USITC 2009b). No category for special-purpose fibers was identified for imports or exports.

Exposure

Occupational exposure to glass fibers by inhalation is the major issue of concern. However, the general population also may be exposed to glass wool fibers in insulation and building materials or in the air near manufacturing facilities or near building fires or implosions. Homeowners engaged in home remodeling projects potentially are exposed to insulation materials through the removal and replacement of existing products; however, no estimates were found of the number of individuals potentially exposed through these activities, or of exposure levels. No information was found on the environmental occurrence of glass fibers or on exposure levels for specific glass-fiber products. The available data suggest that air concentrations of glass fibers in indoor environments do not increase significantly after installation of insulation or from passage of air through ducts lined with glass fibers (NTP 2009).

Occupational exposure may occur during the manufacture of glass wool products, and end users of such products may be exposed during activities such as installation, removal, fabrication, or other work with

glass wool outside the manufacturing environment (NTP 2009). Data from the U.S. Economic Census (USCB 2005) indicate that in 2002, 19,318 workers (15,788 in manufacturing) were employed within the North American Industrial Classification System (NAICS) code 327993, which “comprises establishments primarily engaged in manufacturing mineral wool and mineral wool (i.e., fiberglass) insulation products made of such siliceous materials as rock, slag, and glass or combinations thereof.” Based on the proportions of glass wool to other mineral wools used in the production of insulation products in North America, it is likely that the majority of the workers were involved in the manufacture of glass fibers. The U.S. Bureau of Labor Statistics reported that about 53,000 workers were employed by insulation contractors in 2000 and that nearly 31,000 workers were employed as “insulation workers” within the NAICS code 238310 (Drywall and Insulation Contractors) in 2007 (BLS 2008). In addition, about 150,000 workers involved in other construction trades, such as drywall installers, carpenters, and heating and cooling specialists, install insulation and are periodically exposed to glass wool insulation materials (Maxim *et al.* 2003). The Occupational Safety and Health Administration estimated that in 1992, 185,000 full-time-equivalent construction workers were employed in the U.S. residential insulation trades (Lees *et al.* 1993).

Workplace airborne fiber exposure levels in the United States generally are measured by a standardized method developed by the National Institute for Occupational Safety and Health and used in its current form for asbestos and other fibers since 1994 (NIOSH 1994). NIOSH Method 7400 (with A or B fiber-counting rules) uses phase-contrast optical microscopy (PCOM) to count fibers deposited on an air-sampling filter (NTP 2009, Quinn *et al.* 2005). For counting purposes, Method A rules define a fiber as having a length of greater than 5 µm and an aspect ratio of at least 3:1 (diameter is not specified), and Method B rules define a fiber as having a length of greater than 5 µm, an aspect ratio of at least 5:1, and a diameter of less than 3 µm. Although these methods do not necessarily specify a minimum fiber diameter, the theoretical limit of resolution for optical microscopy of fibers is 0.25 µm; therefore, fibers less than 0.25 µm in diameter will not be counted. Based on how fibers are defined for counting purposes and on the limitations of PCOM technology, these methods do not count all sizes of fibers collected, but rather a small subset within the very broad range of sizes typically present in any given sample (Quinn *et al.* 1996, 2005).

Other fiber definitions have been proposed. Quinn *et al.* (1996) described three definitions by other research groups based on rationales for biologic activity of fibers and proposed their own exposure index: they defined “hypothetically active fibers” (HAF) (i.e., fibers having carcinogenic potential) as being over 5 µm long and less than 6 µm in diameter, with an aspect ratio of at least 3:1. Quinn *et al.* (2000) examined the potential effect of the use of different counting rules on fiber-exposure data. Fibers in air samples collected in eight U.S. glass-fiber production facilities across a wide range of manufacturing processes and products were counted and sized via electron microscopy, and a total fiber size distribution was obtained for each air sample. The ratio between HAF fibers (as defined above) and NIOSH 7400 B fibers was calculated for five samples with geometric mean diameters ranging from 0.1 to 1.73 µm. The ratios ranged from 7.91 to 0.26. These results demonstrate that the choice of fiber counting rules can have a large impact on estimated levels of exposure to glass fibers, which in some instances could result in considerable underestimation of exposure to biologically important fibers.

Analytical data reported for glass-fiber manufacturing operations generally show higher air fiber concentrations for the production of smaller-diameter fibers than for the production of larger-diameter

ter fibers (NTP 2009). In a U.S. study of insulation glass fibers and special-purpose fibers, fiber concentrations in smaller-diameter-fiber operations were many orders of magnitude higher than concentrations in larger-diameter-fiber (insulation glass) operations; in addition, more of the fibers generated in the smaller-diameter-fiber operations were of respirable size (Dement 1975). Physical characteristics of the production plant, such as the physical layout of the equipment, room size, and local ventilation, can also affect the potential for exposure. Studies of U.S. manufacturing facilities reported maximum concentrations of 1.01 fibers/cm³ in an individual sample for insulation-wool manufacturing and 21.9 fibers/cm³ as a mean value for special-purpose-fiber manufacturing (NTP 2009).

For finished products, the potential for exposure depends on the accessibility of individual fibers to the air. Because fibers within a bulk fiber product are trapped by the surrounding material, only the fibers on the surface of the product can become aerosolized. Mechanical handling of products during manufacture, such as stacking, folding, rolling, and chopping, can increase aerosolization of fibers. The geometric mean diameter of airborne fibers increases with the use of oil and binders (Quinn *et al.* 2005), and oil generally is more effective than binders in reducing aerosolization (NTP 2009). The geometric mean diameter of airborne fibers decreases as the nominal diameter of the product being handled decreases (Quinn *et al.* 2005).

Nonmanufacturing occupational exposure levels for end users of glass wool products typically are higher than exposure levels in fiber-manufacturing environments. Exposure levels during installation of insulation vary depending on the product and the task performed. In a comprehensive survey of exposure from residential insulation installation in the early 1990s, workers were monitored during insulation operations in 107 houses in 11 states, and fiber exposure levels were assessed by NIOSH method 7400 B rules. Respirable-fiber concentrations during installation of glass wool batt insulation in homes ranged from 0.02 to 0.41 fibers/cm³, with a mean of 0.14 fibers/cm³. The installation of loose fiberglass insulation with a binder resulted in mean exposures of 0.55 fibers/cm³ for the installer and 0.18 fibers/cm³ for the feeder. The highest exposures were noted for installation of loose insulation without binder; exposure levels ranged from 1.32 to 18.4 fibers/cm³ (mean = 7.67 fibers/cm³) for installers and from 0.06 to 9.36 fibers/cm³ (mean = 1.74 fibers/cm³) for feeders (Lees *et al.* 1993).

In another study, average fiber exposure levels for all activities associated with the installation of commercial and residential insulation (except the blowing of thermal insulation into attics) ranged from 0.003 to 0.13 fibers/cm³ for respirable fibers and from 0.01 to 0.14 fibers/cm³ for total fibers (only fibers < 1 µm in diameter were counted). For various tasks during blowing of attic insulation, average respirable-fiber exposure levels ranged from 0.31 to 1.8 fibers/cm³, and total fiber levels ranged from 0.37 to 2.8 fibers/cm³. For blowers (the task with the highest exposure levels), individual respirable-fiber exposure levels ranged from 0.67 to 4.8 fibers/cm³, and total fiber levels ranged from 0.86 to 5.8 fibers/cm³ (Esmen *et al.* 1982).

Data on exposure to glass fibers during glass wool removal are limited; however, exposure levels appear to be lower than those associated with installation, resembling levels seen in fiber manufacturing operations (Yeung and Rogers 1996).

Regulations

U.S. Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Fine mineral fiber emissions from facilities manufacturing or processing glass (of average diameter ≤ 1 µm) are listed as a hazardous air pollutant.

New Source Performance Standards: Manufacturers of wool fiberglass are subject to provisions for the control of particulates as prescribed in 40 CFR 60.292 and 293.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 15 mg/m³ for total fibers; = 5 mg/m³ for respirable fibers (based on regulation of "particulates not otherwise regulated").

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) limit = 1 fiber/cm³ for respirable fibers. (For comparison, the TLV for asbestos = 0.1 fiber/cm³.)

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) for "fibrous glass dust" = 3 fibers/cm³ (TWA) for fibers with diameter ≤ 3.5 µm and length ≥ 10 µm; = 5 mg/m³ (TWA) for total fibers. (For comparison, the REL for asbestos = 0.1 fiber/cm³ (TWA) for fibers > 5 µm in length.)

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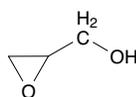
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Glycidol

CAS No. 556-52-5

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)



Carcinogenicity

Glycidol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to glycidol caused tumors at many different tissue sites in mice and rats. Administration of glycidol by stomach tube increased the incidences of benign and/or malignant tumors of the mammary gland (adenoma, fibroadenoma, or adenocarcinoma) in rats of both sexes and female mice, the forestomach (papilloma or carcinoma) in rats of both sexes and male mice, the thyroid gland (follicular-cell adenoma or carcinoma) and the brain (glioma) in rats of both sexes, the Harderian gland (adenoma or adenocarcinoma) in mice of both sexes, and the skin (squamous-cell papilloma or carcinoma, basal-cell tumors, or sebaceous-gland adenoma or adenocarcinoma) in mice of both sexes and male rats. Also observed in rats were cancer of the Zymbal gland (carcinoma) and testis (mesothelioma of the tunica vaginalis) and intestinal tumors (adenomatous polyps or adenocarcinoma) in males and tumors of the mammary gland (fibroadenoma or adenocarcinoma), oral cavity (papilloma or carcinoma), and clitoral gland (adenoma, adenocarcinoma, or carcinoma) in females. In mice, oral exposure to glycidol also caused cancer of the uterus (carcinoma or adenocarcinoma) and subcutaneous tissue (sarcoma or fibrosarcoma) in females and tumors of the lung (alveolar/bronchiolar adenoma or carcinoma) and the liver (mainly carcinoma) in males (NTP 1990, IARC 2000). Also possibly related to glycidol exposure were cancer of the glandular stomach (fibrosarcoma) in female rats and cancer of the urinary bladder (carcinoma) and testis (sarcoma of the epididymis) in male mice.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to glycidol.

Properties

Glycidol is an epoxide alcohol that is a colorless, slightly viscous liquid at room temperature (IARC 2000). It is miscible with water, alcohols, esters, ketones, ethers, and aromatics and almost insoluble in aliphatic hydrocarbons. Glycidol may decompose upon exposure to moisture (Akron 2009). Physical and chemical properties of glycidol are listed in the following table.

Property	Information
Molecular weight	74.1 ^a
Specific gravity	1.115 at 20°C/4°C ^a
Boiling point	160°C at 760 mm Hg ^a
Log K_{ow}	-0.95 ^b
Water solubility	1000 g/L at 20°C ^b
Vapor pressure	0.9 mm Hg at 25°C ^a
Vapor density relative to air	2.15 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Glycidol is a member of a class of chiral molecules that are important intermediates in the industrial synthesis of pharmaceutical products and other biologically active substances and in production of flavoring and sweetening agents and insecticides. It has been used in the pharmaceutical industry since the 1970s; before then, it was used solely for research purposes (Sharpless 2001). Glycidol is used as a stabilizer in the manufacture of vinyl polymers and natural oils and as an intermediate in the synthesis of glycerol, glycidyl ethers, and amines. It is also used as an alkylating agent, demulsifier, and dye-leveling agent and for sterilizing milk of magnesia (IARC 2000, HSDB 2009). The glycidol structure is present in two commercially important groups of derivatives, glycidyl ethers and glycidyl esters, neither of which is prepared directly from glycidol (NTP 1990).

Production

In 2009, glycidol was produced by one manufacturer each in the United States and East Asia (SRI 2009) and was available from 19 suppliers, including 12 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of glycidol were found. Reports filed from 1986 through 1998 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of glycidol totaled 10,000 to 500,000 lb; no reports were filed in 2002. In 2006, the reported quantity was over 500,000 lb (EPA 2009).

Exposure

The primary routes of potential human exposure to glycidol are inhalation, eye and dermal contact, and ingestion. Heating causes the dehydration of glycol configurations in glycerol and sugars to form glycidol; however, the quantities formed during cooking are assumed to be low (Hindso Landin *et al.* 2000). Glycidol is a metabolite of 3-monochloropropane-1,2-diol (Jones 1975), a chloropropanol found in many foods and food ingredients, including soy sauce and hydrolyzed vegetable protein (Huang *et al.* 2005, Retho and Blanchard 2005). Glycidol was detected in the urine of rats exposed to 1-bromopropane by inhalation (Ishidao *et al.* 2002). Occupational exposure to glycidol could occur through inhalation. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 4,872 workers (in 88 facilities and 10 occupations in the Chemicals, Allied Products and Fabricated Metal Products industries), including 580 women, potentially were exposed to glycidol (NIOSH 1990).

Regulations

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 50 ppm (150 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 25 ppm (75 mg/m³).
Immediately dangerous to life and health (IDLH) limit = 150 ppm.

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Hepatitis B Virus

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HBV

Carcinogenicity

Hepatitis B virus (HBV) is known to be a human carcinogen based on sufficient evidence from studies in humans.

Cancer Studies in Humans

Numerous epidemiological cohort and case-control studies conducted in populations differing by race or ethnicity and in various geographic regions have demonstrated that chronic HBV infection causes liver cancer (hepatocellular carcinoma). These studies generally used relatively sensitive and specific serological markers to assess chronic HBV infection. The association between chronic hepatitis B and hepatocellular carcinoma remained strong after adjustment for hepatitis C infection and potential confounding factors such as use of alcohol and tobacco, medical history factors, and dietary exposure to aflatoxin (in areas where aflatoxin contamination of food is common). A meta-analysis of the combined results of 32 studies published between 1993 and 1997 reported a summary odds ratio of 13.7 (95% confidence interval = 12.2 to 15.4) for development of hepatocellular carcinoma among people chronically infected with HBV (as assessed by the presence of HBV surface antigen in the blood) (Donato *et al.* 1998, NTP 2003).

Cancer Studies in Experimental Animals

HBV infects a limited range of hosts, primarily humans and great apes (Tennant 2001); therefore, studies in experimental animals are limited. In chimpanzees, HBV infection does not appear to increase the risk of liver cancer (Muchmore *et al.* 1990). In studies with transgenic mice carrying HBV genes, liver cancer developed in some, but not all, strains that produced high levels of viral surface antigen or X protein (described below, under Properties), but not in strains expressing the entire HBV genome (NTP 2003).

Studies on Mechanisms of Carcinogenesis

Hepatocellular carcinoma usually emerges after 30 years of chronic HBV infection. During the decades of chronic infection, liver cells undergo many changes as a consequence of ongoing viral replication. Viral DNA becomes integrated into the host cells' DNA through non-homologous recombination, and the presence of these viral DNA sequences may contribute to development of cancer through multiple steps, by any of several mechanisms. Expression of genes that regulate tissue growth may be altered through *cis*-activation. Viral DNA also may be integrated into the growth-regulatory genes themselves, causing mutation. Integration of viral DNA may result in truncation at the 3' end of the gene coding for the middle surface antigen or the X protein, resulting in production of novel proteins capable of *trans*-activation. The majority of HBV-positive hepatocellular carcinomas contain HBV DNA sequences that code for *trans*-activator proteins. Viral integration also may result in general instability of chromosomal DNA. Chromosome allele loss appears to be more frequent in HBV-positive hepatocellular carcinomas than in HBV-negative hepatocellular carcinomas (NTP 2003).

It also has been suggested that some HBV proteins, such as the surface antigens and the X protein, may contribute to tumor formation. In transgenic mice, overproduction of the HBV large surface antigen leads to persistent inflammation, production of oxygen radicals, and DNA damage. The X protein may activate viral and host-cell promoters and signal transduction pathways, inhibit DNA repair, and affect the cell cycle and apoptosis. High levels of the X protein may transform immortalized mouse fibroblast (3T3) cells (NTP 2003).

Properties

HBV is an enveloped DNA virus that infects hepatocytes, causing hepatitis B (Blum *et al.* 1983). It is a member of the *Hepadnaviridae* family, which includes the genera *Orthohepadnavirus* (infecting mammals) and *Avihepadnavirus* (infecting birds). The hepadnaviruses have a characteristic partially double-stranded DNA genome,

which is held in a circular conformation by a short, cohesive overlap between the 5' ends of the two strands (Ganem and Schneider 2001). The HBV genome codes for seven proteins: viral DNA polymerase, the core protein (HBcAg), the precore protein, the X protein, and three viral envelope (surface antigen) proteins, large (L), middle (M), and small (S) (NTP 2003). The virion has an icosahedral nucleocapsid, composed of core protein enclosing the viral genome. The nucleocapsid is surrounded by an envelope 42 nm in diameter, which contains (in order of decreasing abundance) the L, M, and S proteins. L is thought to specify the virus's host range, by recognizing cell surface receptors, and S is the immunodominant component of the envelope. The functions of the precore and X proteins are unknown. However, it has been proposed that X affects a variety of cell processes, which may in turn significantly affect hepatocyte gene expression, cell survival, and viral replication. The precore protein is cleaved to form a soluble protein (HBeAg), which is secreted from infected cells and may be detected in the blood of infected individuals (Seeger and Mason 2000, Ganem and Schneider 2001).

Infection, Prevention, and Treatment

HBV infection can cause acute or chronic hepatitis B. Acute hepatitis B is characterized by tissue changes, including hyperplasia, inflammation, and cell death, which appear to result from the host's immune response to HBV antigen (IARC 1994). Chronic hepatitis B, defined as the presence of circulating HBV surface antigen (HBsAg) for over six months, develops in individuals with acute hepatitis B who are not able to clear the virus. The risk of chronic hepatitis B among HBV-infected individuals appears to depend on the status of the immune system at the time of infection and is much higher in HBV-infected infants and children than in HBV-infected adults. About 70% to 90% of infants infected before one year of age develop chronic hepatitis B, whereas the risk of chronic infection among HBV-infected adults is 5% to 10% (IARC 1994, Hollinger and Liang 2001). In chronic hepatitis B, the patient's immune response to HBV results in cycles of cell death and regeneration that may progress to fibrosis of the liver and cirrhosis (replacement of normal liver tissue with bands of fibrous tissue surrounding nodules of regenerating liver tissue) (Hollinger and Liang 2001).

HBV infection can be prevented by screening of the blood supply, reduction of contact with potentially contaminated fluids in health-care settings, and vaccination. The Occupational Safety and Health Administration has established a bloodborne pathogens standard, based on the concept of universal precautions, which requires that body fluids and materials be treated as infectious (OSHA 1992). Recombinant hepatitis B vaccines, which contain HBsAg (produced by genetically engineered yeast cells), have been available in the United States since the 1980s and are recommended for all infants and for individuals at high risk (Hollinger and Liang 2001). Hepatitis B is treated with immunomodulators (drugs that affect the immune system and are not specific for HBV), antiviral drugs, and combination therapy with both drug types; however, these drugs have limited efficacy (Hollinger and Liang 2001, Schalm *et al.* 2002).

Detection

HBV infection is confirmed by detection of HBV proteins, antibodies against HBV proteins, or HBV DNA in the blood. The detection of different proteins and antibodies against these proteins are indicators of different stages of infection. The presence of HBsAg indicates acute or chronic HBV infection, whereas the presence of anti-HBsAg antibodies indicates immunity (due to resolved infection or vaccination) (Hollinger and Dienstag 1995). Strictly speaking, chronic HBV infection is defined by detection of serum HBsAg in two tests six

months apart; however, this criterion is not practical for most epidemiological studies. Because adults who are not carriers of HBV are highly unlikely to test positive for HBsAg, a single positive test result is considered a valid indicator of chronic carrier state in epidemiological studies. Assays approved by the U.S. Food and Drug Administration include enzyme immunoassays or radioimmunoassays for HBsAg, anti-HBsAg antibody, and anti-HBcAg antibody (FDA 2002).

Exposure

The major routes of HBV transmission are parenteral (primarily by injection or transfusion), through sexual contact, from mother to infant at the time of birth, and through health-care practices (Hollinger and Liang 2001). In U.S. surveillance studies conducted in 1992–93, most cases resulted from heterosexual transmission (41%), followed by intravenous drug use (15%) and homosexual transmission (9%); however, 31% of HBV infections were not associated with any known risk factors (CDC 2002). The risk of HBV transmission via transfusion in the United States has been estimated at 1 in 63,000 (Glynn *et al.* 2000); donor education, donor screening, and improved laboratory testing procedures have helped to decrease the risk. In areas where HBV infection is endemic, an important route of transmission is from mother to infant.

Worldwide, about two billion people have been infected with HBV, and over 350 million have chronic hepatitis B. The prevalence of chronic infection varies geographically, ranging from low (less than 2%) in Western Europe, Australia, and North America, to intermediate (2% to 7%) in parts of Southern and Eastern Europe, the Middle East, Japan, West Asia through the Indian subcontinent, and parts of Central and South America, to high (8% or more) in Africa, Asia east of the Indian subcontinent, the Pacific Basin, the Amazon Basin, the Arctic rim, the Asian republics previously part of the Soviet Union, and parts of the Middle East (WHO 2000). In the United States, data from the National Health and Nutrition Examination Survey indicate that the prevalence of HBV infection (both chronic and resolved) decreased from 5.5% for 1976 through 1980 to 4.9% for 1988 through 1994 (McQuillan *et al.* 1999).

The incidence of acute HBV is decreasing in the United States, largely as a result of declining incidence among homosexual men and intravenous drug users, screening of blood products, and vaccination; the incidence decreased from 13.8 per 100,000 in 1987 to 3.3 per 100,000 in 1998. In 2000, the incidence of acute hepatitis B was higher in males than females and highest among individuals aged 25 to 39 (Goldstein *et al.* 2002). The Centers for Disease Control and Prevention (CDC) believed the number of reported symptomatic cases to be much smaller than the actual number of new infections. In particular, infections among infants and young children are likely to be underestimated, because most infections in this age group are asymptomatic. CDC estimated that between 1995 and 1999, 105,000 new infections per year occurred in the United States (McQuillan *et al.* 1999).

Regulations

Food and Drug Administration (FDA)

Regulations have been established to guard against the spread of hepatitis B through donation of blood, serum, and human immune globulin, including requirements for donor screening, product testing, and product labeling.

Each donation of blood, plasma, or serum to be used in preparing a biological product shall be tested for the presence of hepatitis B surface antigen.

21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of hepatitis B.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been developed for employers to develop and adhere to exposure control plans for bloodborne pathogens.

An employer shall make the hepatitis B vaccine available to employees who have had exposure to pathogenic microorganisms.
 All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.
 First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Public Health Service (PHS)

Regulations have been established to control the spread of hepatitis from hemodialysis treatment.

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Hepatitis C Virus

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HCV

Carcinogenicity

Hepatitis C virus (HCV) is known to be a human carcinogen based on sufficient evidence from studies in humans.

Cancer Studies in Humans

In epidemiological research, numerous cohort and case-control studies conducted in populations differing by race or ethnicity and in var-

ious geographical locations have demonstrated that chronic HCV infection causes liver cancer (hepatocellular carcinoma) (NTP 2003). A meta-analysis of 32 studies published between 1993 and 1997 reported a summary odds ratio of 11.5 (95% confidence interval = 9.9 to 13.3) (Donato *et al.* 1998), meaning that patients with chronic HCV infection were 11.5 times as likely as uninfected individuals to develop hepatocellular carcinoma. These studies generally used relatively sensitive and specific serological markers (anti-HCV antibodies or HCV RNA in the blood) to assess chronic HCV infection. The association between HCV and hepatocellular carcinoma was independent of hepatitis B virus (HBV) infection, and it remained when studies controlled for potential confounders such as the use of alcohol or tobacco. A number of recent studies have investigated whether some genotypes of HCV may be more potent carcinogens than others. Although the results are not entirely consistent, the evidence generally supports the hypothesis that HCV genotype 1b is more strongly associated with hepatocellular carcinoma than are other HCV genotypes. A number of recent case-control studies and one cohort study have linked HCV infection to increased risk of B-cell lymphoma; however, many of these studies had relatively small sample sizes, and all were hospital-based (NTP 2003). In 1994, the International Agency for Research on Cancer classified HCV as carcinogenic to humans based on sufficient evidence of carcinogenicity in humans (IARC 1994).

Cancer Studies in Experimental Animals

Studies of HCV in experimental animals are limited, because the only animals known to be susceptible to HCV infection are chimpanzees and tree shrews. Liver cancer (hepatocellular carcinoma) was reported in one chimpanzee that had been infected with HCV for seven years, but not in HCV-infected tree shrews (Linke *et al.* 1987, Muchmore *et al.* 1988, Xie *et al.* 1998). Hepatocellular carcinoma also developed in a few lines of transgenic mice carrying HCV genes; the cancer was observed primarily in males producing either the HCV core protein or low levels of the complete HCV polyprotein (components of the HCV virus, as discussed under Properties, below) (Moriya *et al.* 1998, Koike *et al.* 2002, Lerat *et al.* 2002).

Studies on Mechanisms of Carcinogenesis

The mechanism(s) by which HCV causes liver cancer has not been determined. HCV may cause cancer directly or indirectly, the latter as a result of liver inflammation and regeneration associated with chronic hepatitis. As an RNA virus, HCV does not integrate into the DNA of the hepatitis patient's cells; therefore, direct mechanisms of carcinogenesis would most likely involve the effects of viral protein on cell growth (Fong *et al.* 1991). The HCV core protein is the current leading suspect, based on its role in regulating cellular promoters of gene expression and proto-oncogenes and on the studies in transgenic mice mentioned above. Studies with cell cultures have shown that the HCV core protein cooperates with the *ras* oncogene to transform primary rat embryo fibroblasts to a tumorigenic phenotype (Ray *et al.* 1996). The roles of other HCV proteins in causing liver cancer remain largely unexplored. HCV-related liver cancer almost always arises in the presence of cirrhosis of the liver, suggesting the importance of indirect mechanisms such as inflammation, fibrosis, and hepatocyte regeneration in the development of cancer (Craig *et al.* 1991, Bralet *et al.* 2000). It is hypothesized that cirrhosis results in hepatocellular carcinoma when nodules within the cirrhotic liver become dysplastic (i.e., precancerous cells develop within the nodules) (Takayama *et al.* 1990). Several studies (though not all) have reported an association between HCV-associated liver cancer and β -catenin gene mutations (which are associated with other types of

cancer); however, these studies were based on small numbers of tumors (Huang *et al.* 1999, Laurent-Puig *et al.* 2001, Ueta *et al.* 2002).

Properties

HCV is an enveloped RNA virus, which causes most non-B viral hepatitis that is transmitted parenterally (i.e., by injection, transfusion, or other contact with body fluids). It is a member of the *Flaviviridae* family of viruses and has a particle size of about 50 nm in diameter (He *et al.* 1987). The positive-sense RNA genome (9,600 nucleotides) codes for production of a polyprotein (3,000 amino acids); enzymes produced by the virus and the host cell then cleave the polyprotein into the smaller structural and nonstructural proteins that make up the mature virus particle. The structural proteins, which are incorporated into the viral envelope, consist of the core (nucleocapsid) protein and two glycoproteins (E1 and E2). The nonstructural proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B) serve as enzymes essential for protein processing and RNA replication; their functions include protease, nucleotide triphosphatase, RNA helicase, and RNA polymerase activity (Rosenberg 2001).

Replication of HCV often results in random mutations that are not corrected by the RNA polymerase because it lacks a proofreading function. As a result, the genomes of HCV strains show extensive variability. However, some regions of the genome are more variable than others, and classification of HCV genotypes is based on differences in the less variable regions of the genome. HCVs can be divided into six phylogenetically distinct groups designated as clades (groups of genotypes that share a common ancestor). Within the clades, a number of subtypes (individual genotypes) have been defined (Simmonds *et al.* 1993, Bukh *et al.* 1995, Simmonds 1995, Robertson *et al.* 1998). All known types of HCV have the potential to cause serious liver disease.

Infection, Prevention, and Treatment

HCV can cause acute or chronic hepatitis. Acute hepatitis C usually is characterized by elevated or fluctuating levels of alanine transaminase (ALT). People with acute hepatitis C either have no symptoms (60% to 70%) or have mild clinical disease symptoms: 10% to 20% have nonspecific symptoms, such as nausea, vomiting, anorexia, or abdominal pain, and 20% to 30% may become jaundiced. The average time from exposure to symptoms is six to seven weeks (MMWR 1998). Most people infected with HCV (75% to 80%) go on to develop chronic hepatitis C. Individuals with chronic hepatitis C are the source for all new infections and are at increased risk for chronic liver disease, cirrhosis, and liver cancer (Bonkovsky and Mehta 2001). Chronic hepatitis is associated with chronic liver injury and inflammation. Liver injury appears to be a result of the patient's immune reaction to the virus, rather than damage by the virus itself. Chronic infection usually results in progressive fibrosis of the liver, which may progress to cirrhosis and other disease states. In the United States, HCV is the leading cause of liver disease and may account for 8,000 to 10,000 deaths per year. As of 1996, most HCV-infected individuals were between 30 and 49 years of age; thus, the number of deaths could substantially increase during the next 20 to 30 years, as this group reaches the age at which complications from liver disease usually occur (MMWR 1998, Alter *et al.* 1999).

HCV infection can be prevented by screening of the blood supply and reduction of contact with potentially contaminated fluids in health-care settings. The Occupational Safety and Health Administration has established a bloodborne pathogens standard, based on the concept of universal precautions, which requires that body fluids and materials be treated as infectious (OSHA 1992). Currently, HCV is treated with interferon-based therapies, and no vaccine is available.

Detection

HCV infection usually is confirmed by detection of antibodies against HCV proteins or by detection of HCV RNA. Anti-HCV antibodies are detected by serological assays, which have become more sensitive and specific. HCV RNA usually is detected by tests based on the polymerase chain reaction.

Exposure

The major route of HCV transmission is through contaminated blood. The major risk factor for infection is illegal intravenous drug use, which accounts for 60% of acute HCV infections in adults. Since the screening of blood and blood products for HCV began in the 1990s, blood transfusion has accounted for only a small percentage of adult HCV cases (about 3%). Other routes of transmission include sexual, perinatal, familial (at low rates), and through health-care practices, including transmission by contaminated equipment or supplies, from patient to patient (at low rates), and through occupational exposure (at low rates). In U.S. surveillance studies from 1983 to 1996, no epidemiological risk factors were identified for at least 10% of the cases of acute hepatitis C (Alter *et al.* 1999, Major *et al.* 2001).

The worldwide prevalence of HCV seropositivity based on published studies that used both enzyme immunoassays and supplemental testing is about 3% (170 million individuals). Prevalence varies geographically, ranging from 0.01% to 0.1% in the United Kingdom and Scandinavia to 17% to 26% in Egypt. Prevalence rates are unknown for much of Africa and parts of South America (Wasley and Alter 2000).

In the United States, the third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1994) found that about 3 million to 4 million people were infected with HCV, based on anti-HCV assays (Alter *et al.* 1999). However, the annual incidence of HCV infection declined from 180,000 in the mid 1980s to 28,000 by 1995, probably as a result of testing of blood donors and decreased numbers of cases among intravenous drug users (Alter 1997). Based on NHANES data for 1999 through 2002, about 4.1 million people (95% confidence interval = 3.4 million to 4.9 million) were anti-HCV-positive, with peak prevalence (4.3%) among individuals aged 40 to 49 years. A large percentage (85.1%) of anti-HCV-positive individuals aged 20 to 59 years had a risk factor such as abnormal serum ALT levels, a history of injection drug use, or a history of blood transfusion before 1992 (Armstrong *et al.* 2006).

Regulations

Food and Drug Administration (FDA)

Regulations have been established to guard against the spread of hepatitis C through donation of blood, serum, and human immune globulin, including requirements for donor screening, product testing, and product labeling.

Regulations in 21 CFR 1270 and 1271 prescribe procedures, including donor screening and tissue testing, to ensure that tissues intended for human transplant or other human cells, tissues, and cellular and tissue-based products are free of hepatitis C.

Each donation of blood or blood product to be used in preparing a biological product shall be tested for the presence of hepatitis C surface antigen.

Occupational Safety and Health Administration (OSHA)

All work-related needlestick injuries and cuts from sharp objects that are contaminated with another person's blood or other potentially infectious material must be recorded.

First-aid training program trainees must have adequate instruction in the value of universal precautions for preventing infectious diseases.

Comprehensive regulations have been developed for employers to develop, and adhere to, exposure-control plans for bloodborne pathogens.

Public Health Service (PHS)

Regulations have been established to control the spread of hepatitis from hemodialysis treatment.

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Heterocyclic Amines (Selected)

Also known as HCAs

Introduction

Heterocyclic amines (HCAs) are formed during the cooking of meat, by condensation of creatinine with amino acids. Four individual HCAs are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* (in separate listings):

- 2-Amino-3,4-dimethylimidazo[4,5-f]quinoline (MeIQ) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) was first listed in the *Eleventh Report on Carcinogens* (2004).
- 2-Amino-3-methylimidazo[4,5-f]quinoline (IQ) was first listed in the *Tenth Report on Carcinogens* (2002).
- 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) was first listed in the *Eleventh Report on Carcinogens* (2004).

The profiles for these four HCAs follow. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for each HCA. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to all four listed HCAs and therefore is combined into one section following the discussions of cancer studies.

Note on Cancer Studies of Selected HCAs in Humans

Epidemiological evidence suggests that consumption of well-done or grilled meat may be associated with increased cancer risk in humans. However, the presence of an individual HCA in cooked meat is highly correlated with the presence of other HCAs and with many other constituents, including protein, animal fat, nitrosamines, and substances other than HCAs formed during cooking, such as polycyclic aromatic hydrocarbons. Furthermore, the carcinogenic effects of these HCAs may be inhibited or enhanced by many factors, including interactions of HCA mixtures. It is therefore difficult for human epidemiological studies to establish associations between cancer risk and specific HCAs. For each of these four selected HCAs, the data from epidemiological studies are insufficient to evaluate whether the increased cancer risk is due specifically to consumption of that particular HCA in food (NTP 2002).

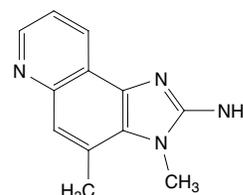
2-Amino-3,4-dimethylimidazo[4,5-f]-quinoline

CAS No. 77094-11-2

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQ



Carcinogenicity

MeIQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

Oral exposure to MeIQ caused tumors at several different tissue sites in mice and rats. In mice of both sexes, MeIQ increased the combined incidence of benign and malignant forestomach tumors (papilloma, squamous-cell carcinoma, and sarcoma). In female mice, it also caused cancer of the cecum and colon (adenocarcinoma) and increased the combined incidence of benign and malignant liver tumors (fibrosarcoma and hepatocellular adenoma and carcinoma). In rats of both sexes, MeIQ increased the combined incidence of benign and malignant colon tumors (adenoma and adenocarcinoma) and caused cancer of the oral cavity and Zymbal gland (squamous-cell carcinoma). In addition, MeIQ caused skin cancer (squamous-cell carcinoma) in male rats and cancer of the mammary gland (adenocarcinoma) in female rats (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQ. In one case-control study, MeIQ intake was associated with increased risks for rectal and colon cancer but not for urinary-bladder or kidney cancer (Augustsson *et al.* 1999).

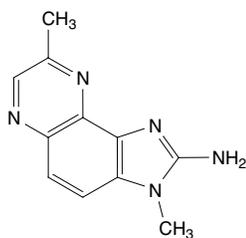
2-Amino-3,8-dimethylimidazo[4,5-f]quinoxaline

CAS No. 77500-04-0

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as MeIQx



Carcinogenicity

MeIQx is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

MeIQx caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to MeIQx increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice and rats of both sexes and the combined incidence of benign and malignant lung tumors (adenoma and adenocarcinoma) in female mice. It also caused lymphoma and leukemia in male mice. In rats, orally administered MeIQx also increased the combined incidence of benign and malignant Zymbal-gland tumors (sebaceous-gland adenoma and squamous-cell papilloma and carcinoma) in both sexes, and it caused skin cancer in males and cancer of the clitoral gland in fe-

males (squamous-cell carcinoma in both cases). Newborn mice exposed to MeIQx by intraperitoneal injection developed benign liver tumors (hepatocellular adenoma). In cynomolgus monkeys, MeIQx administered by stomach tube for 84 months did not cause cancer. This finding was attributed to a low level of metabolic activation of MeIQx via N-hydroxylation in this species; however, the study period may not have been long enough for detection of tumors (NTP 2002).

In rats, administration of N-hydroxy-MeIQx (a metabolite of MeIQx) by intraperitoneal injection caused soft-tissue tumors at the injection site (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to MeIQx. Case-control studies (one study for each tissue site) suggested that MeIQx may increase the risk of benign colon tumors (adenoma) (Sinha *et al.* 2001) and lung cancer (Sinha *et al.* 2000b). MeIQx intake was not associated with cancer risk in case-control studies of urinary-bladder, kidney, or colon cancer (Augustsson *et al.* 1999). The results for breast cancer were conflicting, with two studies reporting increased risk (De Stefani *et al.* 1997, Sinha *et al.* 2000a) and one study reporting decreased risk (Delfino *et al.* 2000).

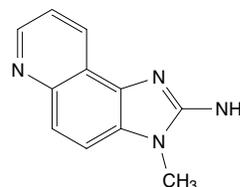
2-Amino-3-methylimidazo[4,5-f]quinoline

CAS No. 76180-96-6

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as IQ



Carcinogenicity

IQ is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

IQ caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. In rats of both sexes, oral exposure to IQ caused cancer of the liver (hepatocellular carcinoma), large intestine (adenocarcinoma), and Zymbal gland (squamous-cell carcinoma). It also caused cancer of the mammary gland (adenocarcinoma) and clitoral gland (squamous-cell carcinoma) in female rats and cancer of the small intestine (adenocarcinoma) and skin (squamous-cell carcinoma) in male rats. In mice of both sexes, oral exposure to IQ increased the combined incidences of benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma), forestomach (papilloma and squamous-cell carcinoma), and lung (adenoma and adenocarcinoma). Newborn mice administered IQ by intraperitoneal injection developed benign and malignant liver tumors (hepatocellular adenoma and carcinoma). Male rats administered IQ by intrarectal infusion developed cancer of the colon (carcinoma) and skin (squamous-cell carcinoma) and benign liver tumors (hepatocellular adenoma). In cynomolgus mon-

keys, IQ administered orally caused liver cancer (hepatocellular carcinoma) (NTP 1999).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to IQ. One case-control study suggested that IQ intake increased the risk of breast cancer (De Stefani *et al.* 1997), but another case-control study found no association between IQ and cancer of the colon, rectum, urinary bladder, or kidney (Augustsson *et al.* 1999).

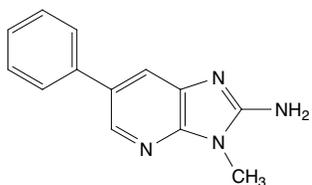
2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine

CAS No. 105650-23-5

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as PhIP



Carcinogenicity

PhIP is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting genotoxicity data.

Cancer Studies in Experimental Animals

PhIP caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral exposure to PhIP caused lymphoma in mice of both sexes and in male rats. In rats, it also caused prostate cancer (carcinoma) and cancer of the small intestine and colon (adenocarcinoma) and in males and mammary-gland cancer (adenocarcinoma) in females. In a short-term study using mice with a mutation that made them susceptible to intestinal and mammary-gland tumors, oral administration of PhIP increased the combined incidence of benign and malignant tumors of the small intestine (adenoma and adenocarcinoma) in males. PhIP administered to newborn male mice by intraperitoneal injection caused benign liver tumors (hepatocellular adenoma) (NTP 2002).

N-hydroxy-PhIP (a metabolite of PhIP) administered by intraperitoneal injection caused intestinal polyps in *Apc* knockout mice (which are unable to produce the tumor-suppressor protein APC). In ACI/Seg rats (a strain with high spontaneous incidence of prostate cancer) administered *N*-hydroxy-PhIP by intraperitoneal injection, the incidences of colon tumors and rare urinary-bladder tumors were increased, though not significantly (NTP 2002).

Cancer Studies in Humans

The evidence from epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to PhIP. Case-control studies suggest that PhIP may increase the risk of breast or stomach cancer. However, the association with stomach cancer was based on only one study (De Stefani *et al.* 1998), and the association with breast cancer was found in two of three studies (De Stefani *et al.* 1997, Delfino *et al.* 2000, Sinha *et al.* 2000a). No association between PhIP intake and cancer risk was found in case-

control studies of urinary-bladder, kidney, lung, colon, or prostate cancer (Augustsson *et al.* 1999, Norrish *et al.* 1999, Sinha *et al.* 2000b). PhIP intake was associated with increased risk of benign colon tumors (adenoma) in one study, but the risk was not significantly increased when the statistical analysis controlled for intake of other HCAs (Sinha *et al.* 2001).

Heterocyclic Amines (Selected)

Studies on Mechanisms of Carcinogenesis

Studies have consistently shown that MeIQ, MeIQx, IQ, and PhIP cause mutations in most test systems, including bacteria, rodents exposed *in vivo*, and cultured rodent and human cells. Moreover, compared with other well-known mutagens, such as benzo[a]pyrene, these HCAs show a high degree of potency. MeIQ, MeIQx, IQ, and PhIP also caused sister chromatid exchange, micronucleus formation, and unscheduled DNA synthesis, and most of these HCAs induced DNA damage and chromosomal aberrations in *in vivo* studies in rodents and in *in vitro* studies with human and rodent cell cultures (IARC 1993, NTP 2002).

When ingested by humans or administered orally to experimental animals, HCAs are readily absorbed and rapidly distributed. They are metabolized by both phase I (activation) and phase II (conjugation) enzymes. The major phase I activation pathway is *N*-hydroxylation by the enzyme CYP1A2 (a member of the cytochrome P450 family). Further activation by phase II enzymes, in the liver or in other tissues, is necessary for formation of the aryl nitrenium ion, which ultimately binds to DNA (NTP 2002).

HCA-induced DNA adducts have been characterized and detected in humans and other mammalian species both *in vitro* and *in vivo*, and the major adduct for each HCA is similar in all species examined. In humans, DNA adducts form at dietarily relevant levels of HCA exposure and usually are present at higher frequencies than in rodents administered an equivalent dose. HCA-induced adducts have been identified in human colon tissue, breast tissue, and prostate tumors. The DNA adduct data indicate that metabolic activation of HCAs is more efficient in humans than in experimental animals and that rapid acetylators (individuals who produce an efficient version of the enzyme *N*-acetyltransferase) may be at higher risk of cancer than slow acetylators (individuals who produce less-efficient versions of this enzyme). In studies with experimental animals, HCA-induced DNA adducts were formed in a dose-dependent manner and were associated with carcinogenesis (NTP 2002).

Mutations involving guanine (such as G:C to T:A transversions) have been detected in proto-oncogenes and tumor-suppressor genes, including *Ki-ras*, *Ha-ras*, *Apc*, *p53*, and β -*catenin*, suggesting that HCA-induced adducts are involved. The observed mutation patterns provide evidence for a mutational profile or "fingerprint" for PhIP-induced colon tumors and MeIQ-induced forestomach and Zymbal-gland tumors in mice (NTP 2002).

Properties

MeIQ, MeIQx, IQ, and PhIP are heterocyclic amines formed by condensation of creatinine with amino acids during the cooking of meat. (Creatinine is a breakdown product of creatine, an important constituent of muscle.) All of these HCAs share a common imidazole ring structure with an exocyclic amino group and, therefore, are known chemically as amino-imidazozaarenes. Most HCAs, including MeIQ, MeIQx, and IQ, are fully planar aromatic structures with no bulky out-of-plane functionalities; however, PhIP possesses a phenyl moiety that is not necessarily coplanar with the main bicyclic imidazopyridine. All of these HCAs occur as crystalline solids and are soluble in

dimethylsulfoxide or methanol. Physical and chemical properties of MeIQ, MeIQx, IQ, and PhIP are listed in the following table.

Property	MeIQ	MeIQx	IQ	PhIP
Molecular weight	212.2	213.2	198.2	224.1
Color	pale orange to brown	yellow-green	light tan	gray-white
Melting point (°C)	296 to 298	295 to 300	> 300	327 to 328
Log K_{ow}	1.822			
Extinction coefficient	48,000 at 265 nm	41,000 at 273 nm	51,500 at 264 nm	19,400 at 316 nm

Sources: IARC 1993, Knize *et al.* 1995.

Use

MeIQ, MeIQx, IQ, and PhIP have no known commercial uses (IARC 1993).

Production

MeIQ, MeIQx, IQ, and PhIP are produced in small quantities for research purposes (IARC 1993). They are formed naturally during the cooking of muscle-derived foods (meat and fish) as by-products of the Maillard (or browning) reaction (Robbana-Barnat *et al.* 1996, Felton *et al.* 2000). It is postulated that the amino-imidazo part of HCAs is formed from creatine, while the remaining parts of the compound are likely formed from Strecker degradation products, such as pyridines or pyrazines, which are formed in the Maillard reaction between hexose sugars and amino acids (Jagerstad *et al.* 1984, Skog *et al.* 1998). Formation of HCAs in food reportedly is affected by temperature, processing time, acidity, precursor concentrations, and types of amino acid present (Keating *et al.* 1999). In general, higher temperatures and longer cooking times increase the amount of HCAs produced (Knize *et al.* 1994, Skog *et al.* 1995). HCA formation also increases with cooking methods that use direct or efficient transfer of heat from the source to the food; frying or grilling of muscle meats produces more HCAs than do indirect-heat methods such as stewing, steaming, or poaching (Layton *et al.* 1995).

Exposure

Exposure to MeIQ, MeIQx, IQ, or PhIP occurs primarily through the consumption of cooked meats; however, HCAs have also been detected in processed food flavorings, beer, wine, and cigarette smoke. Dietary exposure to total HCAs has been estimated to range from less than 1 to 17 ng/kg of body weight per day (Layton *et al.* 1995).

Total HCA concentrations in cooked meat generally range from less than 1 to about 500 ng/g (0.001 to 0.5 ppm) but usually are less than 100 ng/g (Layton *et al.* 1995, Sinha *et al.* 1995, 1998a, 1998b, Knize *et al.* 1998, Salmon *et al.* 2000). Pan residues usually contain higher HCA concentrations than the meat itself; therefore, gravy made from meat drippings and grease may have relatively high concentrations of HCAs. In four studies (reviewed by Keating *et al.* 1999), total daily HCA intakes (including MeIQx, IQ, and PhIP, but not MeIQ) ranged from 160 to 1,800 ng per person. In general, the dietary intake of these four HCAs is greatest for PhIP, followed by MeIQx, IQ, and MeIQ.

As discussed above (under Production), the concentration of HCAs in food is a function of cooking method; dietary intake is therefore a function of cooking method, doneness preference, and consumption frequency (Keating *et al.* 1999). Several studies have reported on possible methods for reducing dietary HCA (Skog *et al.* 1997, Knize *et al.* 1999, Salmon *et al.* 2000). Effective methods include using cooking temperatures below 200°C (392°F), turning meat more frequently during cooking, precooking meat in a microwave oven for at least two minutes and draining off the liquid before conventional

cooking, and applying marinades before grilling. However, some marinades are more effective than others; PhIP and MeIQx concentrations were reduced by teriyaki sauce or turmeric-garlic sauce, but increased by a honey barbecue sauce (Nerurkar *et al.* 1999).

Occupational exposure to HCAs may occur by inhalation of aerosolized particles formed during the cooking process. PhIP and MeIQx were detected in smoke condensate formed during frying of beef patties and bacon (Thiébaud *et al.* 1995), and MeIQx was detected in aerosol from cooking of stir-fried fish (Yang *et al.* 1998). PhIP was detected in airborne particles, diesel-exhaust particles, and incineration ash from garbage-burning plants (Manabe *et al.* 1993).

Specific exposure information for each of these four HCAs follows.

MeIQ

MeIQ is found less frequently in food and generally at lower concentrations than are other HCAs, including MeIQx, PhIP, and IQ. The highest concentrations were detected in cooked fish, ranging from 0.03 to 72 ng/g; the concentrations were highest in grilled sun-dried sardines and lower in fried or broiled fish (IARC 1993, Lynch *et al.* 1995). MeIQ was found at low levels or was not detectable in cooked beef, pork, or chicken; various studies reported concentrations ranging from 0.02 ng/g (in pork) to 1.7 ng/g (in well-done bacon) (Johansson and Jagerstad 1994, Lynch *et al.* 1995). It was also detected in gravy, coffee beans, and cigarette smoke. In a Swiss population, daily MeIQ intake was estimated to be 0.6 ng/kg of body mass (Zimmerli *et al.* 2001).

MeIQx

MeIQx has been detected in beef, pork, chicken, and fish. The highest concentrations were found in well-done grilled chicken, beef (hamburger or steak), and bacon. Very-well-done grilled or barbecued chicken contained 9 ng/g, and very-well-done oven-broiled or pan-fried skinless, boneless chicken breasts contained 3 ng/g (Sinha *et al.* 1995). In one study, MeIQx concentrations in beef ranged from nondetectable to 8.2 ng/g in steak and from nondetectable to 4.6 ng/g in hamburger patties, depending on the cooking method and degree of doneness (Sinha *et al.* 1998b). Another study found that fish contained about 1.2 ng/g (Johansson and Jägerstad 1994). Pork, other than bacon, contains very little MeIQx; MeIQx was detected at 0.9 to 18 ng/g in bacon and 1.4 to 27 ng/g in bacon fat (Gross *et al.* 1993). MeIQx also occurs in processed food flavors (bouillon and gravy concentrates) and wine. In three large U.S. cohort studies (two Nurses' Health Studies and the Health Professionals Follow-Up Study), estimated mean daily intake of MeIQx ranged from 33 to 44.8 ng/g of food consumed (Byrne *et al.* 1998). Daily MeIQx intake was estimated to be 2.61 ng/kg of body mass (Layton *et al.* 1995). MeIQx also has been found in air and surface water.

IQ

IQ was originally isolated from broiled fish, fried ground beef, and beef extracts. It has since been detected in fried chicken, fried eggs, fried fish, broiled ground beef, minute steaks, meatballs, pork chops, and cigarette smoke condensate. Reported concentrations in foods range from less than 0.1 to more than 150 ng/g, with most less than 1 ng/g (IARC 1993, Skog *et al.* 1995, Chiu *et al.* 1998). However, Sinha *et al.* (1998b) did not detect IQ in hamburgers, steaks, or roast beef cooked by varying methods to three levels of doneness. The highest reported IQ concentration occurred in broiled sun-dried sardines. Daily IQ intake from meat and fish was estimated to be 0.28 ng/kg of body mass (Layton *et al.* 1995).

PhIP

PhIP is the most abundant HCA detected in foods and has been found in beef, pork, chicken, lamb, and fish. The highest concentrations were detected in very-well-done grilled chicken; however, concentrations varied considerably from study to study. High concentrations (over 100 ng/g) were found in well-done steak and hamburgers. Concentrations of PhIP in fish varied greatly according to the type of fish and method of cooking; one study reported levels ranging from 1.7 to 73 ng/g in salmon cooked at 200°C by various methods (pan broiled, oven cooked, or barbecued) for various lengths of time (Gross and Grüter 1992), but another study (Skog *et al.* 1997) reported substantially lower levels (0.02 to 2.2 ng/g) for cod and Baltic herring fillets pan fried at temperatures ranging from 150°C to 225°C. PhIP was found at lower concentrations in pork (0.1 to 2.3 ng/g). It was also detected in processed food flavors, beer, and wine at concentrations ranging from 0.01 to 480 ng/g and in cigarette smoke. In the same three large U.S. cohort studies cited above for MeIQx, mean daily PhIP intake ranged from 285.5 to 457 ng/day (Byrne *et al.* 1998). Daily PhIP intake was estimated to be 17 ng/kg of body mass (Layton *et al.* 1995). PhIP has also been found in air and surface water.

Regulations

No regulations or guidelines relevant to reduction of exposure to heterocyclic amines were identified.

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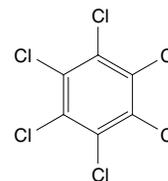
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Hexachlorobenzene**CAS No. 118-74-1**

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

**Carcinogenicity**

Hexachlorobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to hexachlorobenzene caused tumors in several rodent species and at two different tissue sites. Dietary administration of hexachlorobenzene caused liver tumors (hepatocellular tumors) in female rats and mice and in hamsters of both sexes. In hamsters of both sexes, it also caused blood-vessel tumors in the liver (hemangioendothelioma) and benign thyroid-gland tumors (follicular-cell adenoma) (IARC 1979, Smith and Cabral 1980).

Since hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, additional studies in rats have been identified. Dietary exposure caused benign and malignant liver tumors (bile-duct adenoma and hepatocellular carcinoma) and benign blood-vessel tumors in the liver (hemangioma) in females and benign kidney tumors (adenoma) in both sexes. Perinatal exposure to hexachlorobenzene followed by dietary exposure for up to 130 weeks caused benign liver tumors (hepatocellular adenoma) in females, benign parathyroid-gland tumors (adenoma) in males, and benign adrenal-gland tumors (pheochromocytoma) in both sexes (IARC 1987, 2001).

Cancer Studies in Humans

At the time hexachlorobenzene was listed in the *Third Annual Report on Carcinogens*, no epidemiological studies had evaluated the relationship between human cancer and exposure specifically to hexachlorobenzene. Since then, several case-control studies, mostly of breast cancer, have been published. The International Agency for Research on Cancer concluded that there was inadequate evidence in humans for the carcinogenicity of hexachlorobenzene (IARC 2001). No association between exposure to hexachlorobenzene and breast cancer risk was found in five small case-control studies or three larger studies that assessed hexachlorobenzene exposure by measuring it in biological samples obtained close to the time of breast-cancer diagnosis. In a fourth large study, which assessed exposure from banked serum samples collected prior to diagnosis, breast-cancer risk was higher among women with higher serum concentrations of hexachlorobenzene than among women with the lowest serum concentrations, based on sampling close to the time of diagnosis; however, no dose-response relationship was observed. No significant associations between serum hexachlorobenzene concentration and risk of cancer at other tissue sites were found; however, only one study was available for each tissue site.

Since the IARC (2001) review, a number of additional studies have been conducted, mainly of breast cancer and non-Hodgkin's lymphoma. Two studies reported significantly higher serum hexachlorobenzene levels in women with breast cancer than in control subjects (Charlier *et al.* 2003, 2004), but four other studies found no significant association between serum hexachlorobenzene level and breast cancer (Lopez-Carrillo *et al.* 2002, Pavuk *et al.* 2003, Iwasaki *et al.* 2008, Itoh *et al.* 2009). One study of non-Hodgkin's lymphoma found a significant dose-related risk associated with serum hexachlorobenzene (Spinelli *et al.* 2007), and two studies found a significantly increased risk among patients with high Epstein-Barr virus antibody titers (also associated with non-Hodgkin's lymphoma) (Hardell *et al.* 2001, 2009). However, no association with non-Hodgkin's lymphoma was observed in a study using banked serum samples collected up to 20 years prior to diagnosis and analyzed for hexachlorobenzene (Cantor *et al.* 2003) or in a multicenter study of lymphoma patients using blood levels of hexachlorobenzene measured close to the time of diagnosis (Cocco *et al.* 2008).

Properties

Hexachlorobenzene is a chlorinated aromatic hydrocarbon that exists as a white needle-like crystalline solid at room temperature (HSDB

2010). It is practically insoluble in water, sparingly soluble in cold alcohol and carbon tetrachloride, and soluble in benzene, chloroform, ether, and carbon disulfide. It is stable under normal temperatures and pressures (Akron 2010). It is combustible but it does not ignite readily. When hexachlorobenzene decomposes, it emits highly toxic fumes of hydrochloric acid, other chlorinated compounds, carbon monoxide, and carbon dioxide. Physical and chemical properties of hexachlorobenzene are listed in the following table.

Property	Information
Molecular weight	284.8
Density	2.044 g/cm ³ at 23°C
Melting point	231.8°C
Boiling point	325°C
Log <i>K</i> _{ow}	5.73
Water solubility	4.7 × 10 ⁻⁶ g/L at 25°C
Vapor density relative to air	9.83

Source: HSDB 2010.

Use

No commercial uses of hexachlorobenzene as an end product in the United States were identified (ATSDR 2002). Previously, it was used as a seed-treatment fungicide for onions, sorghum, wheat, and other grains (IARC 1979). All registered pesticide uses in the United States were voluntarily cancelled in 1984 (ATSDR 2002). Hexachlorobenzene was also used as a chemical intermediate in dye manufacturing, in the synthesis of other organic chemicals, and in the production of pyrotechnic compositions for the military. It was used as a raw material for synthetic rubber, as a plasticizer for polyvinyl chloride, as a porosity controller in the manufacture of electrodes, and as a wood preservative (IARC 1979, ATSDR 2002).

Production

Commercial production of hexachlorobenzene in the United States was first reported in 1933 (IARC 1979). In 1975, 3,200 lb of hexachlorobenzene was produced, but it has not been produced commercially in the United States since the late 1970s. In 1972, an estimated 2.5 million to 4.9 million pounds of hexachlorobenzene was produced in the United States as a by-product of production of other chlorinated solvents and pesticides such as tetrachloroethylene, trichloroethylene, carbon tetrachloride, vinyl chloride, atrazine, propazine, simazine, pentachlorophenol, chlorothalonil, and pentachloronitrobenzene. In addition, hexachlorobenzene may be formed during combustion of municipal waste or in waste streams from chlor-alkali and wood-preserving plants (IARC 1979, ATSDR 2002).

In 2002, nine U.S. chemical companies produced hexachlorobenzene for on-site use and processing, as a by-product, or as an impurity (ATSDR 2002). In 2009, hexachlorobenzene was available from 19 suppliers worldwide, including 14 U.S. suppliers (ChemSources 2010). U.S. imports of hexachlorobenzene totaled about 5,400 lb in 1977 and 38,000 lb in 1982 (ATSDR 2002, HSDB 2010). Imports of hexachlorobenzene and dichlorodiphenyltrichloroethane (DDT) (reported together) have generally been low since 1989. However, 2.3 million pounds was imported in 1993 and 4.9 million pounds in 2001, even though neither hexachlorobenzene nor DDT is used in the United States (USITC 2010). Imports were zero in 2007 and 11 lb in both 2006 and 2008. U.S. exports in this category have remained at about 1 million pounds or less since 1989, reaching a low of 7,000 lb in 2008. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hexachlorobenzene totaled 10,000 to 500,000 lb in 1998 and 2002 (EPA 2004).

Exposure

Hexachlorobenzene is highly persistent in the environment and highly resistant to degradation; therefore, the general population may be exposed at low concentrations (ATSDR 2002). When hexachlorobenzene is released to the environment, it may be taken up by plants and animals and can bioaccumulate through the food chain. Hexachlorobenzene has been detected in terrestrial, freshwater, and marine food chains in the Great Lakes and Arctic regions. Populations with the greatest potential for exposure include those who ingest fish caught from contaminated water bodies or who reside near former manufacturing or waste-disposal sites.

According to EPA's Toxics Release Inventory, environmental releases of hexachlorobenzene ranged from over 1 million pounds in 1989 and 1991 to a low of about 12,600 lb in 1997. In 2008, 49 facilities released a total of 50,636 lb of hexachlorobenzene, mostly to on-site and off-site landfills. The majority of releases came from 5 facilities, and 12 facilities reported releases of more than 100 lb (TRI 2010). When hexachlorobenzene is released to air, it tends to remain mainly in the vapor phase and can therefore be transported great distances (for example, from temperate to polar regions). When released to water, hexachlorobenzene is strongly adsorbed to particles and sediment and is not degraded or hydrolyzed (ATSDR 2002). In the Great Lakes region, hexachlorobenzene was found in drinking and surface water and, at higher levels, in soil and sediment. In 1972, it was detected in agricultural soils where it had been used as a pesticide, at lower levels in urban soils, and at higher levels in soils near uncontrolled hazardous-waste sites. It was found at high concentrations in sediments near industrial sites at Galveston Bay, Texas (ATSDR 2002).

In dietary surveys conducted by the U.S. Food and Drug Administration, the frequency at which hexachlorobenzene was detected in foods declined from 9% in the early 1980s to less than 2% in 1994 (ATSDR 2002). Consequently, the U.S. average daily intake of hexachlorobenzene through foods declined by a factor of 5 over this period. In the FDA Total Diet Study, hexachlorobenzene was detected in 229 of 1,748 samples (13%) of 42 different foods; the highest concentration was found in butter (FDA 2006).

Hexachlorobenzene has been detected in the blood of numerous groups of people, especially indigenous populations of Arctic regions, in the blood and breast milk of pregnant and lactating women, and in the placenta and cord blood. Organochlorine compounds were found in maternal blood in circumpolar populations in Greenland, Canada, Alaska, Norway, Sweden, Iceland, Finland, and Russia (Van Oostdam *et al.* 2004). In Arctic Canada, hexachlorobenzene was detected in all samples of maternal blood, and at higher concentrations in blood from Inuit women than from Caucasian women in the region. Cord-blood plasma concentrations showed a similar trend (Butler Walker *et al.* 2003). Breast-milk concentrations of hexachlorobenzene were elevated in populations of women who ate contaminated local fish in New York State and Finland (Greizerstein *et al.* 1999, Kostyniak *et al.* 1999, Fitzgerald *et al.* 2001, Damgaard *et al.* 2006). Hexachlorobenzene was found in all blood samples from pregnant women in an agricultural community in California (Fenster *et al.* 2006). The diet of the Inuit population in Greenland was studied to determine the source of the high and increasing concentration of hexachlorobenzene. The blood levels of hexachlorobenzene in Greenland Arctic populations appeared to correlate with consumption of meals containing seal and whale (Deutch *et al.* 2004, 2006). Hexachlorobenzene was detected in all adipose tissue samples collected at autopsy from Greenlanders (Dewailly *et al.* 1999). Hexachlorobenzene was detected in 98% of the blood samples collected from Akwesasne Mohawk youth living along the St. Lawrence River in New York State and Quebec; levels were somewhat higher in youths who had been breastfed as

infants (Schell *et al.* 2003). In a study of consumers of sport fish in New York State, the mean blood hexachlorobenzene concentration was not significantly greater than that of nonconsumers of sport fish (Bloom *et al.* 2005).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,038 workers at 10 facilities, including 26 women, potentially were exposed to hexachlorobenzene (NIOSH 1990). The largest numbers of exposed workers were chemical technicians (467 workers) and their supervisors (187 workers). Occupations with the highest potential for exposure included fungicide application, organic-chemical synthesis, synthetic-rubber production, seed disinfection, pesticide production, and wood preservation.

Regulations

Department of Transportation (DOT)

Hexachlorobenzene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of hexachlorobenzene is subject to certain provisions for the control of volatile organic compound emissions.
Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Chlorinated benzenes are listed as a toxic pollutant.
Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00028 µg/L; based on fish or shellfish consumption only = 0.00029 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxic characteristic leaching procedure threshold = 0.13 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of hexachlorobenzene = U127, F024, F025, K016, K018, K030, K042, K085, K149, K150, K151.
 Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.001 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.001 mg/L.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.002 mg/m³.

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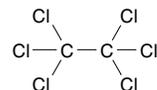
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Hexachloroethane

CAS No. 67-72-1

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)



Carcinogenicity

Hexachloroethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to hexachloroethane caused tumors in two rodent species and at several different tissue sites. Administration of hexachloroethane by stomach tube caused liver cancer (hepatocellular carcinoma) in mice of both sexes and benign and malignant kidney tumors (renal-tubular adenoma and carcinoma) in male rats (NCI 1978, IARC 1979, NTP 1989). The incidence of benign adrenal-gland tumors (pheochromocytoma) also was marginally increased in male rats.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to hexachloroethane. Since hexachloroethane was listed in the *Seventh Annual Report on Carcinogens*, one additional epidemiological study has been identified. In a cohort study of workers at aluminum foundries and smelters in Sweden, no association was observed between cancer incidence and exposure to hexachloroethane (IARC 1999).

Properties

Hexachloroethane is a chlorinated alkane that exists at room temperature as a colorless crystalline solid with a camphor-like odor. It is practically insoluble in water, soluble in ethanol, benzene, chloroform, and oils, and very soluble in diethyl ether and tetrachloroethylene (Akron 2009, HSDB 2009). Hexachloroethane is stable under normal temperatures and pressures and is considered nonflammable; however, it is incompatible or reactive with alkalis and with metals such as zinc, cadmium, aluminum, hot iron, and mercury (NIOSH 2005). Physical and chemical properties of hexachloroethane are listed in the following table.

Property	Information
Molecular weight	236.7 ^a
Specific gravity	2.09 at 20°C/4°C ^a
Melting point	185°C (closed capillary) ^a
Boiling point	186°C at 777 mm Hg (sublimes) ^a
Log <i>K</i> _{ow}	4.14 ^a
Water solubility	50 mg/L at 25°C ^b
Vapor pressure	0.21 mm Hg at 20°C ^a
Vapor density relative to air	8.16 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The applications of hexachloroethane have been extensive; however, industrial uses are diminishing. Hexachloroethane is used primarily in military smoke munitions (e.g., smoke pots, grenades, cartridges, and projectiles used to generate "smoke" or "fog") and in pyrotechnics.

The estimated average annual use of hexachloroethane from 1966 to 1977 at a major facility manufacturing smoke and pyrotechnic devices was 192,802 lb. In the 1970s, about half of the hexachloroethane distributed was used to manufacture military smoke-producing and pyrotechnic devices, 30% to 40% to manufacture degassing pellets to remove air bubbles from molten ore at aluminum foundries, and 10% to 20% as an antihelminthic to control liver flukes in sheep and cattle. The U.S. Food and Drug Administration withdrew approval for the use of hexachloroethane as an antihelminthic in 1971, and it probably is no longer used for this purpose (ATSDR 1997). Its use for degassing aluminum also has been almost completely phased out in the United States (EPA 1999). Other uses in metallurgy include refining alloys, removing impurities from molten metals, recovering metals from ores or smelting products, and as a degassing agent for magnesium; however, the European Union began phasing out the use of hexachloroethane in nonferrous metals in 1998 (EC 1998).

A number of other past uses of hexachloroethane have been identified, but many of these likely have been discontinued or involve the use of only limited quantities. Hexachloroethane is used as a laboratory chemical and as an ingredient in various fungicidal and insecticidal formulations, extreme-pressure lubricants, and plastics (ATSDR 1997, IARC 1999, HSDB 2009). Other past uses include as a moth repellent and in the chemical industry as a polymer additive, a plasticizer for cellulose esters, an accelerator, a vulcanizing agent, a process solvent in rubber manufacturing, a retardant in fermentation processes, and a component of submarine paints, and in the production of some types of synthetic diamonds. It has also been used as a component of fire-extinguishing fluids, an additive in combustible liquids (ignition suppressant), and an inhibitor of the explosiveness of methane and the combustion of ammonium perchlorate (IARC 1979, 1999, HSDB 2009).

Production

Production of hexachloroethane in the United States for commercial distribution began in 1921 and ended in 1967 (IARC 1979, ATSDR 1997). Currently, hexachloroethane is produced as a by-product of industrial chlorination of two-carbon hydrocarbons. It may be used in-house or recycled in feedstock to produce tetrachloroethylene or carbon tetrachloride. In 2009, hexachloroethane was produced by four manufacturers, all in India (SRI 2009) and was available from 35 suppliers, including 20 U.S. suppliers (ChemSources 2009). U.S. imports of hexachloroethane increased from 1.6 million pounds in 1976 to over 2 million pounds in 1977, 2.5 million pounds in 1985, and 4.5 million pounds in 1986 (ATSDR 1997). U.S. imports in the category of hexachloroethane and tetrachloroethane combined have shown an erratic pattern but have tended to decline in recent years, from 689,000 kg (1.5 million pounds) in 1989 to 139,000 kg (306,000 lb) in 2008 (USITC 2009). U.S. exports of hexachloroethane are not expected (ATSDR 1997). Exports in the category of hexachloroethane and tetrachloroethane combined reached a high of 11 million kilograms (25 million pounds) in 2005 and declined rapidly to 167,000 kg (368,000 lb) in 2008 (USITC 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hexachloroethane totaled 10 million to 50 million pounds in 1986 and 1994, 1 million to 10 million pounds in 1990, 500,000 lb to 1 million pounds in 1998, and 10,000 to 500,000 lb in 2002 (EPA 2004). In 2006, the reported quantity was 1 million to 10 million pounds (EPA 2009).

Exposure

The routes of potential human exposure to hexachloroethane are inhalation, dermal contact, and ingestion (ATSDR 1997, NCI 1978).

The general population can be exposed to hexachloroethane in the environment at relatively low levels, primarily from ambient air but possibly also from drinking water (ATSDR 1997). According to EPA's Toxics Release Inventory, environmental releases of hexachloroethane from 1988 to 2007 ranged from a high of about 360,000 lb in 1994 to a low of 1,015 lb in 2004. These data, however, do not include releases at military facilities, which are exempt from reporting (TRI 2009). Although data on releases at military facilities are limited, a major military training facility in Fort Irwin, California, was reported to have released up to 6,683 kg (14,700 lb) of hexachloroethane from smoke devices from 1982 to 1984 (ATSDR 1997). In addition to releases to air from military uses, hexachloroethane may be released through combustion and incineration of chlorinated wastes, from hazardous waste sites, and in small amounts during chlorination of sewage effluent prior to discharge and during chlorination of raw water during drinking-water treatment.

Hexachloroethane is relatively persistent in the environment and has been detected in the atmosphere and in drinking water at low levels. When released to air, hexachloroethane is stable and is not expected to react with hydroxyl radicals or ozone (ATSDR 1997, HSDB 2009). Typical background atmospheric levels in the Northern Hemisphere ranged from 5 to 7 ppt (48 to 68 ng/m³). When released to surface water or soil, hexachloroethane is most likely to volatilize or to be adsorbed to soil or sediments; thus, it will have moderate to low mobility in soil. It has been detected in drinking-water wells near a toxic waste dump in Tennessee (median concentration = 0.26 µg/L). Hexachloroethane has also been detected at low levels in surface water, biota, ambient soil, sediments, and commercial food products (ATSDR 1997). Between 1977 and 1979, it was detected in 4 of 14 raw water samples from drinking-water supply sources. In 1975, it was measured in finished drinking water at a concentration of 4.4 µg/L (HSDB 2009). In the early 1980s, it was detected in only 1 of 882 ambient surface water samples and in none of 116 fish samples (based on data in EPA's STORET database). However, fish collected in Ohio in 1980 and 1981 contained hexachloroethane at a concentration of 0.1 mg/kg, and fish from Lake Michigan were reported to contain hexachloroethane, although concentrations were not reported (HSDB 2009). Some bioconcentration in fish has been reported; however, biomagnification through the food chain is unlikely, because hexachloroethane is rapidly metabolized by fish (ATSDR 1997).

Organochlorine pollutants, including hexachloroethane, were measured in human follicular fluid, serum, and seminal plasma in couples undergoing *in vitro* fertilization in Canada (Younglai *et al.* 2002). Hexachloroethane was found in over half of the samples of follicular fluid, at a mean concentration of 232 pg/mL.

Occupational exposure to hexachloroethane can occur through inhalation or dermal contact. Military and civilian personnel working with smoke or pyrotechnic devices that contain hexachloroethane could be exposed. Most of the hexachloroethane in a smoke pot or grenade is used up by the smoke-producing reaction, but small amounts (5% or less) remain after the smoke has formed and could result in further exposure. One study reported hexachloroethane concentrations in smoke ranging from 0.64 to 1.26 mg/m³. Plasma concentrations of hexachloroethane in workers exposed to hexachloroethane in loading and packing operations for smoke munitions production rose from 0.08 ± 0.14 µg/L to 7.3 ± 6.0 µg/L after more than five weeks of work in those areas, despite the use of protective equipment, including disposable overalls and compressed-air-fed visors or full-facepiece masks with filters (ATSDR 1997).

Other occupational exposure to hexachloroethane may occur during its manufacture, transportation, or use. Elevated amounts of hexachloroethane in the air can result when it is used in aluminum

foundries as a degassing agent. Industries that may have used hexachloroethane include real estate, paper and allied products, lumber and wood products, and amusement and recreation services (NIOSH 1978). Occupations with potential exposure to hexachloroethane include cleaners and charwomen, millwrights, miscellaneous machine operatives, plumbers and pipefitters, and electricians. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 8,516 workers, including 576 women, potentially were exposed to hexachloroethane in seven industries (Business Services; Machinery, Except Electrical; Chemicals and Allied Products; Primary Metal; Electric and Electronic Equipment; Transportation by Air; and Printing and Publishing) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Hexachloroethane is considered a hazardous substance, and special requirements have been set for transporting hexachloroethane in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of hexachloroethane is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.
Water Quality Criteria: Based on fish and shellfish and water consumption = 1.4 µg/L; based on fish and shellfish consumption only = 3.3 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 3.0 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of hexachloroethane = U131, F024, F025, K016, K030, K073.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.
Permissible exposure limit (PEL) = 1 ppm (10 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm (10 mg/m³).
Immediately dangerous to life and health (IDLH) limit = 300 ppm.
Listed as a potential occupational carcinogen.

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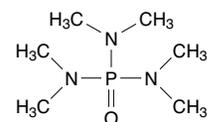
Hexamethylphosphoramide

CAS No. 680-31-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as HMPA or hexamethylphosphoric triamide



Carcinogenicity

Hexamethylphosphoramide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to hexamethylphosphoramide by inhalation caused nasal tumors, which are rare in this species. Inhalation of hexamethylphosphoramide caused benign and malignant nasal tumors (papilloma, epidermoid carcinoma, adenoid squamous carcinoma, transitional-cell carcinoma, and adenocarcinoma) in rats of both sexes (IARC 1977, Lee and Trochimowicz 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to hexamethylphosphoramide.

Properties

Hexamethylphosphoramide is a phosphoric acid amide derivative that exists at room temperature as a colorless to light-amber mobile liquid with a spicy odor. It is miscible with water and most organic liquids but is immiscible with high-boiling-point saturated hydrocarbons. It is stable at normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of hexamethylphosphoramide are listed in the following table.

Property	Information
Molecular weight	179.2 ^a
Specific gravity	1.03 at 20°C ^a
Freezing point	5°C to 7°C ^a
Boiling point	233°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	0.28 ^b
Water solubility	1,000 g/L ^b
Vapor pressure	0.03 mm Hg at 25°C ^c
Vapor density relative to air	6.18 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Hexamethylphosphoramide was formerly used by its major U.S. producer only as a processing solvent for aromatic polyamide fiber (Kevlar); however, it now has a number of additional uses (IARC 1977, 1999, HSDB 2009). It is used as a solvent for other polymers, for gases, and for organic and organometallic reactions in research laboratories. It is also used as a polymerization catalyst, a stabilizer against thermal degradation in polystyrene, an additive to polyvinyl and polyolefin resins to protect against degradation by ultraviolet light, and a color-enhancing agent for the thiocyanate-cobalt complex used for cobalt detection. Hexamethylphosphoramide has been used as an antistatic agent and a flame retardant and deicing additive for jet fuels. It also can be used as a flame-retarding additive in lithium-ion batteries; however, it reduces the performance of the battery (Izquierdo-Gonzales *et al.* 2004).

Production

In 2009, hexamethylphosphoramide was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 21 suppliers, including 14 U.S. suppliers (ChemSources 2009). No data on U.S. production, import, or export volumes were found.

Exposure

The routes of potential human exposure to hexamethylphosphoramide are inhalation, ingestion, and dermal contact (HSDB 2009). The major source of exposure is probably occupational; however, the general population potentially could be exposed through release of hexamethylphosphoramide to the environment. No environmental releases of hexamethylphosphoramide were reported in the U.S. Environmental Protection Agency's Toxics Release Inventory (TRI 2009). Hexamethylphosphoramide exists in the air solely in the vapor phase and will be degraded by photochemically produced hydroxyl radicals, with a half-life of 2 hours (HSDB 2009). If released to soil or water, hexamethylphosphoramide may leach rapidly in soil and sediments. It is not expected to bioconcentrate in aquatic organisms.

EPA evaluated the potential for release of hexamethylphosphoramide into the soil, surface water, and groundwater near a site in Spruance, Virginia, where hexamethylphosphoramide was used and disposed of (EPA 1980, 1999). In 1976, disposal of hexamethylphosphoramide from the facility directly into the James River was documented. Up to 48 lb per month was discharged; however, surface-water concentrations downstream from the discharge point

were approximately 0.5 ppb, the lower limit of detection. Solid wastes from the Spruance site containing hexamethylphosphoramide also had been disposed of in Anniston, Alabama; evaluation of the disposal site indicated detectable quantities of hexamethylphosphoramide in a drainage ditch downstream from the disposal site, in an on-site groundwater well, and in a well upgradient from the disposal site, but not in Anniston's drinking water. The waste was removed from the disposal site, and remedial actions were taken at the site to mitigate risks of human exposure (EPA 1980). In 1999, hexamethylphosphoramide was identified as a contaminant in groundwater monitoring wells at the Spruance facility site, in nearby off-site wells at concentrations of up to 480 µg/L, and in surface water downgradient from the facility at a concentration of 0.17 µg/L (EPA 1999). Potential levels of off-site exposure were below levels of concern for human health and the environment.

Occupational exposure may occur among workers involved in the production of hexamethylphosphoramide or in its use as a solvent or chemical additive or in the packaging of consumer products. The National Institute for Occupational Safety and Health estimated that up to 90% of about 5,000 people who worked in U.S. laboratories that used hexamethylphosphoramide might have been exposed (NIOSH 1975). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 700 workers (in the Business Services industry), including 51 women, potentially were exposed to hexamethylphosphoramide (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Hexamethylphosphoramide is listed as a potential occupational carcinogen.

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Human Papillomaviruses: Some Genital-Mucosal Types

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as HPVs

Carcinogenicity

Some human papillomaviruses (HPVs) of the genital-mucosal type are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

In epidemiological research, numerous case-control studies have consistently reported strong associations between cervical cancer and infection with HPV-16, HPV-18, or "high-risk" HPVs as a class (discussed under Properties, below). Moreover, several case-control studies have provided strong evidence of positive associations between cervical cancer and other individual HPVs, including HPV types 31, 33, 35, 39, 45, 51, 52, 58, and 59 (Muñoz 2000). Cohort studies have demonstrated that infection with HPV-16 or with high-risk HPVs as a class occurs before the development of high-grade cervical intraepithelial neoplasia (CIN), which is thought to be a precursor of invasive cancer. The evidence from cohort studies is weaker for individual high-risk viruses, possibly because they are less common; among these, the evidence for an association with cervical cancer appears to be strongest for HPV-18 (NTP 2003). It is unlikely that the association between HPV infection and cervical cancer is due to other factors that could increase the risk of cancer, because many studies included these factors in their analysis, and because of the large magnitude of the odds ratios estimated in the case-control studies. Thus, these studies demonstrate that some genital-mucosal HPVs cause cervical cancer. In addition to the association with cervical cancer, there is strong evidence that HPV-16 infection is associated with other anogenital cancers, especially cancer of the vulva (NTP 2003). Evidence also suggests associations between HPV infection and some cancers of the head and neck and, especially, the soft palate (oropharynx), tonsils, and back of the tongue and throat (NTP 2003).

Based on testing of tissue specimens from more than 1,000 invasive malignant cervical tumors from women from 22 countries (collected for the International Biological Study of Cervical Cancer), it was estimated that HPV is present in 99.7% of all malignant cervical tumors, suggesting that HPV infection may be necessary for development of cervical cancer (Walboomers *et al.* 1999). Nonetheless, not all individuals infected with HPV develop cervical cancer. Most HPV infections (about 70%) clear within 1 to 2 years, and thus confer little risk of cancer. The specific risk factor for cervical cancer appears to be persistent infection with HPV-16 or other high-risk HPVs. Whether HPV infections persist probably depends both on viral characteristics, such as greater persistence of specific HPV types or variants, and on characteristics of the patient, such as sex-hormone levels, smoking behavior, or immune-system status.

Since human papillomaviruses (some genital-mucosal types) were listed in the *Eleventh Report on Carcinogens*, numerous human cancer studies on HPVs have been published. The International Agency for Research on Cancer concluded that HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 were carcinogenic in humans based on sufficient evidence for the carcinogenicity of HPV-16 in the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx and sufficient evidence for the carcinogenicity of HPV types 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 66 in the cervix. IARC also concluded that there was limited evidence for the carcinogenicity of HPV types 6, 11, and 18 in the vulva, penis, and anus; HPV types 6, 11, 16, and 18 in the larynx; HPV-18 in the vagina; and HPV-16 in the periungual skin (the skin around the fingernails or toenails) (IARC 2007).

Cancer Studies in Experimental Animals

Because HPV infections are specific to humans, experimental animals cannot be infected with them. Many studies have investigated the carcinogenicity of various animal papillomaviruses both in their natural host species and in other species. Studies in monkeys, cattle, rabbits, and sheep have shown that animal papillomaviruses cause cancer in their natural hosts. Studies in transgenic mice carrying HPV genes demonstrated that HPV proteins play a role in the development of abnormal tissue growth (dysplasia) and progression to tumor formation. Transgenic mice expressing some HPV type 16 or 18 genes and producing the corresponding viral proteins developed tumors of the cervix and other tissues (Arbeit *et al.* 1994, Comerford *et al.* 1995).

Studies on Mechanisms of Carcinogenesis

Infection with high-risk HPVs is associated with chromosomal aberrations, including abnormal centrosome numbers, chromosomal imbalances at specific chromosomal regions, and changes in chromosome number, including tetrasomy and other types of aneuploidy (NTP 2003).

HPV can integrate into the DNA of the host cell and can immortalize and transform cells, enabling them to proliferate and form tumors. Most studies on the mechanisms of HPV carcinogenesis have investigated HPV-16 and HPV-18. HPV types 16, 18, 31, and 33 have been shown to transform cells, types 16, 18, and 31 to immortalize cells, and types 16 and 18 to produce proteins that bind to regulatory proteins of the host cell. The HPV proteins E2 and E5 and the long control region of the HPV genome (discussed under Properties, below) play a role in HPV-induced cell transformation. However, the HPV proteins primarily responsible for immortalization and transformation are E6 and E7, as shown in studies with human and rodent cell cultures. Studies with transgenic mice expressing the E6 or E7 gene further support the notion that the E6 and E7 proteins are important in HPV-associated neoplasia. Both the E6 and E7 proteins alter the pathways that regulate tissue growth, by interfering with growth receptors or growth factors; production of cytokines has been shown to be altered in cells infected with HPV-16. The E6 protein increases degradation of the p53 tumor-suppressor protein, thereby interfering with apoptosis. The E7 protein disrupts complexes of the transcription factor E2F with the tumor-suppressor protein pRb and related proteins involved in control of the cell cycle and causes their degradation, altering control of transcription and progression of the cell cycle. The E7 protein has been shown to cause abnormal synthesis and duplication of centrosomes, resulting in abnormal mitotic division.

Properties

HPVs of the genital-mucosal type are DNA viruses that infect the genital skin and genital and non-genital mucosa, sometimes causing genital warts or cervical abnormalities. They are members of the family

Papillomaviridae, which consists of species-specific non-enveloped viruses that infect the squamous epithelium of the skin and mucosal membranes of animals. More than 100 different HPVs had been identified by 2004, including viruses that cause skin warts as well as the genital-mucosal type (Howley and Lowy 2001). The over 40 genital-mucosal HPVs have been classified as either “high risk” or “low risk”; high-risk viruses have been associated with cervical cancer in human epidemiological studies, whereas low-risk viruses have been associated with genital warts or low-grade CIN (abnormal tissue growth in the cervical epithelium that is unlikely to progress to cancer). Most studies have considered HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68 to be high-risk viruses; some studies also include other HPVs, most notably HPV-66. Classification of HPVs is based also on phylogenetic and mechanistic considerations. Most high-risk viruses have DNA sequences highly similar to those of either HPV-16 or HPV-18, suggesting that they are closely related to these types. Studies on the mechanisms of carcinogenesis have shown that high-risk but not low-risk viruses immortalize human keratinocytes (skin cells), interact with the tumor-suppressor proteins pRb and p53, and cause chromosomal aberrations. However, most mechanistic studies have evaluated only a few HPVs, the majority focusing on HPV-16 or HPV-18 and a few on HPV-31 or HPV-33.

HPVs are small (about 52 to 55 nm in diameter), consisting of about 8,000 base pairs of covalently closed, double-stranded DNA. The viral genome consists of a series of open reading frames, each of which is a DNA sequence that codes for an HPV protein, and a long control region, which contains elements that regulate DNA replication and protein synthesis. Productive infection of cells (leading to replication of the virus) is linked to their stages of differentiation. Viral replication can be divided into early and late stages, which occur in cells at different stages of differentiation. Early stages of replication (including attachment of the virus to the cell, entry and uncoating, early gene expression, protein production, and DNA replication) occur in basal cells. These cells are the youngest, least differentiated cells and are located in the lower layers of the epithelium; they are the only dividing cells in the squamous epithelium. Late stages of viral replication, which include the events leading to production of viral particles (late gene expression, production of capsid proteins, vegetative viral DNA replication, and virus assembly and release), occur in the terminally differentiating squamous epithelial cells, which are the oldest, most differentiated cells, in the upper layers of the epithelium. The genes expressed in the early stages of viral replication, designated E1 through E8, are associated with regulation of transcription (e.g., E2) and cellular proliferation (e.g., E6 and E7). The genes expressed in the late stages, designated L1 and L2, encode the two proteins that make up the viral capsid (Howley and Lowy 2001).

Infection, Prevention, and Treatment

Genital-mucosal HPVs infect the cervix, causing lesions of varying severity, including genital warts, low- and high-grade CIN, and invasive cervical cancer (Einstein and Burk 2001). Low-grade CIN (CIN I) is a well-differentiated lesion in which the squamous epithelial cells show alterations characteristic of the cytopathogenic effects of a replicative viral infection, such as the presence of two nuclei or other nuclear abnormalities and koilocytosis (the presence of cells with abnormal nuclei and a hollow appearance resulting from collapse of the cell's internal structure). The alterations seen in CIN I are not usually considered to be precursors of cancer. The majority of CIN I lesions are transient and resolve spontaneously, but a small percentage may progress to high-grade CIN or invasive cancer (Jastreboff and Cymet 2002). Both high-risk and low-risk HPVs can cause low-grade CIN (IARC 1995). High-grade CIN (CIN II or III) is characterized by the

presence of undifferentiated cells above the lower third of the epithelium (extending into the upper layers) and by nuclear crowding, substantial pleomorphism, loss of tissue organization and cellular polarity, abnormal mitotic figures, and larger numbers of atypical cells than observed in low-grade CIN (IARC 1995). High-grade CIN probably results from persistent HPV infection, and it is more likely than low-grade CIN to progress to invasive cancer. (CIN III is also known as carcinoma *in situ*, or noninvasive cancer.) Microinvasive squamous-cell cervical cancer usually arises from high-grade CIN.

Two HPV vaccines are licensed by the U.S. Food and Drug Administration and recommended by the Centers for Disease Control and Prevention (CDC 2010). Both vaccines are effective against HPV types 16 and 18, which are responsible for most cervical cancer, and one of the vaccines is also effective against HPV 6 and 11, which cause genital warts. Both vaccines are given in three doses, with the second dose given one to two months after the first and the third dose six months after the first (CDC 2009). Treatment of HPV infection depends on the severity of the disease and may involve topical applications, interferon-related therapies, or excision of the lesion via laser methods, surgery, or cryotherapy.

Detection

HPV infection is detected by observation of visible lesions or microscopic changes in cells, by detection of HPV DNA, or by detection of antibodies against HPV proteins in the blood. Genital warts (condylomata acuminata) are genital lesions visible to the naked eye; they have a fleshy red appearance and a raised surface that usually extends in papillae. Flat condylomata are flat, nonpapillary lesions; they are more difficult to detect and may be apparent only after swabbing with acetic acid and colposcopic examination, in which they appear as white, flat, shiny lesions. The Papanicolaou (Pap) smear, which involves microscopic examination of stained exfoliated genital cells, detects koilocytosis and other signs of CIN; it is used to screen for cervical cancer by detecting high-grade CIN (Trofatter 1997).

The most sensitive and specific method for detecting HPV infection is to test for HPV DNA. DNA testing can be used to detect a broad spectrum of HPV genotypes (Trofatter 1997). Detection of HPV DNA signifies present exposure or persistent infection resulting from a past exposure. The most sensitive HPV DNA tests are (1) those based on the polymerase chain reaction and (2) the Hybrid Capture assay, which is based on the formation of hybrids between HPV DNA and RNA probes. The most commonly used serological tests for HPV infection measure antibodies (immunoglobulin G) against capsid antigens (most often tested as virus-like particles). Several validation studies have estimated the sensitivity of such serological tests to be approximately 50%, using detection of HPV DNA as a standard (Dillner 2000). Because of their low sensitivity, serological assays are not recommended for diagnostic use, but they are useful for comparison of groups in epidemiological studies, which also commonly use HPV DNA testing. Clinical diagnosis of HPV is most commonly based on the Hybrid Capture 2 assay.

Exposure

Genital-mucosal HPVs are transmitted primarily through sexual contact with infected cervical, vaginal, vulvar, penile, or anal epithelium (IARC 1995). This finding is supported by numerous epidemiological studies demonstrating that HPV infection is associated with behaviors related to sexual activity. Numerous studies of HPV in women have reported a positive association between lifetime number of sex partners and HPV seropositivity (Sun *et al.* 1999, Silins *et al.* 2000) or the presence of HPV DNA (Franco *et al.* 1995, Kjær *et al.* 1997, Lazcano-Ponce *et al.* 2001). Recent sexual activity, the number of sex partners,

frequency of sexual intercourse, and presence of genital warts on sex partners are strong predictors of HPV infection, as indicated by HPV DNA testing (Franco *et al.* 1995, Ho *et al.* 1998). The role of men in carrying HPV infection from one woman to another has been demonstrated in studies showing that cervical cancer is relatively more frequent among wives whose husbands have detectable HPV DNA in their penis or whose husbands have had more extramarital partners (Bosch *et al.* 1996). Penile lesions containing the DNA of high-risk HPVs are frequent among male sex partners of women with CIN (Bleeker *et al.* 2002). There are conflicting reports as to whether HPV is transmitted at birth or perinatally. Infants exposed perinatally to HPV-11, or less commonly to HPV-6, may develop a rare benign tumor of the airway called juvenile-onset recurrent respiratory papillomatosis (Shoultz *et al.* 1997).

HPV infection is one of the most common sexually transmitted diseases. It appears that the majority of those infected have no symptoms, and it is estimated that 20 million people in the United States are infected with HPV (CDC 2001). The percentage of infected individuals (prevalence) is highest among those who are young and sexually active. U.S. epidemiological studies based on HPV DNA testing indicate that between 25% and 40% of sexually active women aged 15 to 25 are infected (Lowy and Howley 2001). Among all U.S. men and women aged 15 to 49, the estimated prevalence of HPV infection (based on HPV DNA testing) is 10% to 20%, whereas only 1% have genital warts, and 4% show cellular abnormalities associated with HPV infection (Koutsky 1997). For most populations of mixed age groups, the prevalence of HPV infection has been estimated at 5% to 15%. HPV-16 appears to be the most prevalent type worldwide (Jastreboff and Cymet 2002). In a study of women aged 18 to 40 with no history of high-grade CIN, among whom the prevalence of HPV was 39%, high-risk HPVs were more common (occurring in 26.7% of women) than low-risk HPVs (occurring in 14.7%) (Peyton *et al.* 2001).

In 2000, CDC estimated the number of new genital HPV cases per year (incidence) to be 5.5 million (CDC 2001). In the general population of Rochester, Minnesota, the average age- and gender-adjusted incidence of genital warts increased from 13 per 100,000 in the early 1950s to 106 per 100,000 in the late 1970s. During this period, the U.S. incidence of other sexually transmitted diseases also increased dramatically (IARC 1995, Shoultz *et al.* 1997). Several follow-up studies reported very high incidences of HPV infection (as detected by HPV DNA testing) among young, sexually active individuals, with three-year cumulative incidences ranging from 43% to 55% (Ho *et al.* 1998, Moscicki *et al.* 2001).

In most women infected with HPV (70%), the infection clears within 12 to 24 months (Franco *et al.* 1999, Dillner 2000). Some studies have suggested that low-risk HPV infections are more likely to regress than are high-risk HPV infections (Franco *et al.* 1999, Elfgren *et al.* 2000). The immune system plays an important role in HPV infection; immunocompromised patients are at increased risk for persistent HPV infection (Lowy and Howley 2001).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to HPVs were identified.

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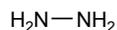
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Hydrazine and Hydrazine Sulfate

CAS Nos. 302-01-2 and 10034-93-2

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Hydrazine and hydrazine sulfate are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to hydrazine or hydrazine sulfate caused tumors in two rodent species at several different tissue sites and by several different routes of administration. Most studies of oral exposure used hydrazine sulfate. Oral exposure to hydrazine sulfate (either in the drinking water or by stomach tube) caused benign and malignant lung tumors (adenoma and adenocarcinoma) in mice and rats of both sexes and liver cancer in mice of both sexes (hepatocellular carcinoma) and in male rats (spindle-cell sarcoma). Intraperitoneal injection of hydrazine caused lung tumors, myeloid leukemia, and lymphoma (reticulum-cell sarcoma) in mice of both sexes (IARC 1974).

Since hydrazine and hydrazine sulfate were listed in the *Third Annual Report on Carcinogens*, additional studies in rodents have been identified. Perinatal exposure to hydrazine sulfate caused lung cancer (adenocarcinoma) in mice as adults (IARC 1987). Exposure to hydrazine by inhalation caused benign or malignant nasal tumors (adenomatous or villous polyps, adenocarcinoma, or squamous-cell papilloma or carcinoma) in rats and benign tumors of the nasal cavity (adenomatous polyps) in male hamsters. A few tumors of the colon (adenocarcinoma, leiomyoma, and papilloma) and thyroid (parafollicular-cell adenoma) also were observed in male hamsters at the highest exposure level and may have been exposure-related (Vernot *et al.* 1985, IARC 1987). Administration of hydrazine sulfate in the drinking water caused liver cancer (hepatocellular carcinoma) in hamsters (IARC 1999).

Cancer Studies in Humans

No excess risk of cancer was found in a small cohort study of 423 men engaged in the manufacture of hydrazine (Roe 1978). Since hydrazine and hydrazine sulfate were listed in the *Third Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer concluded in 1999 that the evidence for the carcinogenicity of hydrazine from studies in humans was inadequate. No excess risk of cancer mortality was found in a follow-up of the Roe cohort (Wald *et al.* 1984, Wald 1985) or in a small retrospective cohort study of 427 workers in a hydrazine plant (Morris *et al.* 1995). Since the 1999 IARC review, studies of two additional cohorts have been identified. A significant dose-response relationship between hydrazine exposure and lung-cancer incidence and mortality and a significant increase in colorectal-cancer incidence were found among aerospace workers, of whom about one fourth potentially were exposed to hydrazine, 1-methylhydrazine, or 1,1-dimethylhydrazine in rocket fuel (Ritz *et al.* 1999, 2006). No association between smoking and hydrazine exposure was observed for a subset of these workers, and risk estimates were adjusted for potentially confounding occupational exposures. No significant association between cancer mortality and potential exposure to hydrazine was found in a retrospective cohort study of workers at a rocket en-

gine testing facility, of whom 315 likely had been exposed to hydrazines (Boice Jr. *et al.* 2006).

Properties

At room temperature, hydrazine is a colorless oily liquid with a penetrating ammonia-like odor, and hydrazine sulfate is a white crystalline solid (HSDB 2009). Hydrazine is miscible with methyl, ethyl, propyl, and butyl alcohols, slightly miscible with hydrocarbons and halogenated hydrocarbons, and insoluble in chloroform and ether. Hydrazine sulfate is soluble in water but practically insoluble in ethanol. Both compounds are thermally unstable (Akron 2009). Physical and chemical properties of hydrazine and hydrazine sulfate are listed in the following table.

Property	Hydrazine	Hydrazine Sulfate
Molecular weight	32.1	130.1
Specific gravity	1.0036 at 25°C/4°C	1.378
Melting point	2.0°C	254°C
Boiling point	113.5°C at 760 mm Hg	NR
Log K_{ow}	-2.07	NR
Water solubility	1,000 g/L	34.1 g/L
Vapor pressure	14.4 mm Hg at 25°C	NR
Dissociation constant (pK_a)	7.96	6.7

Source: HSDB 2009. NR = Not reported.

Use

Hydrazine is used primarily as a chemical intermediate to produce agricultural chemicals and chemical blowing agents, as a corrosion inhibitor and water-treatment chemical, and as a rocket propellant. In the early 1980s, 40% of hydrazine was used in agricultural chemicals, 33% in blowing agents, 15% as a corrosion inhibitor, and 5% as a rocket propellant (ATSDR 1997). It has been used for plating metals on glass and plastics, in fuel cells and solder fluxes, as a reducing agent in electrode-less nickel plating, as a chain extender in urethane polymerizations, and as a reducing agent in extraction of plutonium from nuclear reactor waste. It has also been used to produce photography chemicals, textile dyes, heat stabilizers, explosives, hydrazine sulfate, and antituberculars and other pharmaceuticals (Sax and Lewis 1987, ATSDR 1997, HSDB 2009).

Hydrazine sulfate has been used in refining rare metals, as an antioxidant in soldering flux for light metals, in analytical tests for blood, as a reducing agent in the analysis of minerals and slag, in the preparation of hydrazine hydrate, in the manufacture of chemicals, in condensation reactions, as a catalyst in making acetate fibers, as a fungicide and germicide, in the analysis of minerals, and in the determination of arsenic in metals (HSDB 2009b).

Production

U.S. production capacity for hydrazine hydrate was estimated at 55 million pounds in 1988, and production capacity for hydrazine solutions was 36.3 million pounds in 1992 (IARC 1999). In 2009, hydrazine was produced by three manufacturers worldwide, including one in the United States, and hydrazine sulfate by 14 manufacturers, including one in the United States (SRI 2009). Hydrazine was available from 27 suppliers, including 19 U.S. suppliers, and hydrazine sulfate from 34 suppliers, including 20 U.S. suppliers (ChemSources 2009). U.S. imports in the category "hydrazine and hydroxylamine and their salts" generally increased from 1989 to 2008, reaching a low of 2 million kilograms (4.4 million pounds) in 1993 and a high of 23.5 million kilograms (51.8 million pounds) in 1999 (USITC 2009). During this period, U.S. exports in this category fluctuated but generally declined, from a high of 20.3 million kilograms (44.7 million pounds) in 1997 to a low of 2.4 million kilograms (5.3 million pounds)

in 2008. Reports filed in 1986 and 1990 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of hydrazine totaled 10,000 to 500,000 lb. No reports for hydrazine were filed in 1994 or 1998, but reports filed in 2002 and 2006 indicated quantities of 1 million to 10 million pounds (EPA 2004, 2009). Inventory update reports were filed for hydrazine sulfate only in 1990, indicating a total quantity of 10,000 to 500,000 lb (EPA 2004).

Exposure

The primary routes of potential human exposure to hydrazine are ingestion, inhalation, and dermal contact (HSDB 2009). The exposure potential for the general population is low, but exposure may occur through inhalation of cigarette smoke or ingestion of trace amounts in processed foods. Hydrazine has been detected in cigarette smoke at a concentration of 32 µg per cigarette (PHS 1982). Hydrazine sulfate may be ingested intentionally, as it has been studied as a treatment for cancer (NCI 2008).

Hydrazine and hydrazine sulfate may be released to the environment through production, use, and waste disposal (ATSDR 1997, HSDB 2009). EPA's Toxics Release Inventory reported that in 2007, environmental releases of hydrazine from 23 facilities totaled 16,759 lb, 14,570 lb of which was released by one facility to underground injection wells. Releases of hydrazine sulfate between 1988 and 2003 ranged from 24,000 lb (in 2001) to 356,172 lb (in 1988), with no major long-term trend. Almost all hydrazine sulfate was released to underground injection wells; a small amount was released to air. No releases of hydrazine sulfate were reported after 2003 (TRI 2009). In most environmental media, hydrazine is rapidly degraded by oxidation. High concentrations of hydrazine are toxic to microorganisms, but at low concentrations, biodegradation may occur. Use of hydrazine in boiler water treatment may result in its brief occurrence in discharged waste, where it will be oxidized (ATSDR 1997, HSDB 2009).

Occupational exposure is most likely to occur by inhalation or dermal contact where hydrazine or hydrazine sulfate is produced or used (HSDB 2009). Hydrazine exposure has been documented in the paper, tire-manufacturing, military, and aerospace industries (Helmert *et al.* 2004, Korhonen *et al.* 2004, Ritz *et al.* 2006, Durmusoglu *et al.* 2007). In the vulcanization step of tire manufacturing, hydrazine was measured at concentrations of up to 8.0 mg/m³, resulting in an estimated daily intake of 0.0031 mg/kg of body weight (Durmusoglu 2007). Hydrazine fuels are used for rockets and high-performance military jet aircraft; exposure of workers refueling these planes has been reported (Helmert 2004). The National Aeronautics and Space Administration reported developing a reusable propellant-handler's suit that was expected to be the world's most advanced garment for protection from chemical agents, especially rocket propellants such as hydrazine (Doerr 2001). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 60,490 workers, including 2,841 women, potentially were exposed to hydrazine and that 14,330 workers, including 6,716 women, potentially were exposed to hydrazine sulfate (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Hydrazine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Hydrazine is listed as a hazardous air pollutant.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb for hydrazine.

Urban Air Toxics Strategy: Hydrazine is identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for hydrazine.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for hydrazine.

Threshold planning quantity (TPQ) = 1,000 lb for hydrazine.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of hydrazine = U133.

Hydrazine is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Hydrazine is not permitted in steam in food-treatment processes.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (1.3 mg/m³) for hydrazine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm for hydrazine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm for hydrazine.

Ceiling recommended exposure limit = 0.03 ppm (0.04 mg/m³) (2-h exposure) for hydrazine.

Hydrazine is listed as a potential occupational carcinogen.

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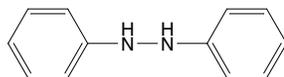
Hydrazobenzene

CAS No. 122-66-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 1,2-diphenylhydrazine



Carcinogenicity

Hydrazobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to hydrazobenzene caused tumors in two rodent species and at several different tissue sites. It caused liver cancer (hepatocellular carcinoma) in female mice and male rats and benign liver tumors (hepatocellular adenoma) in female rats. In rats, it also caused mammary-gland cancer (adenocarcinoma) in females and increased the combined incidence of benign and malignant Zymbal-gland tumors (squamous-cell papilloma and carcinoma) in males (NCI 1978). Since hydrazobenzene was listed in the *Second Annual Report on Carcinogens*, an additional study in mice has been identified. Hydrazobenzene administered by intraperitoneal injection to strain A mice (a strain with a high spontaneous incidence of lung cancer) caused benign lung tumors (alveolar-bronchial adenoma) in males, but not in females (Maronpot *et al.* 1986).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to hydrazobenzene. A number of historical occupational cohort studies of workers in the benzidine-based-dye industry, who may be exposed to hydrazobenzene (a precursor of benzidine), found signif-

icantly increased risks of bladder cancer (de Braud *et al.* 2002). Two case-control studies reported increased risks of bladder cancer among workers with potential exposure to chemical dyes, after controlling for smoking and other variables (Wynder *et al.* 1963, Anthony and Thomas 1970), prompting the National Cancer Institute to evaluate the carcinogenicity of hydrazobenzene in rodents (NCI 1978). In the studies of dye workers, hydrazobenzene exposure was not quantified and could not be distinguished from exposure to other chemicals, including benzidine, 2-naphthylamine, and 4-aminodiphenyl, which are known human carcinogens associated with bladder-cancer risk.

Properties

Hydrazobenzene is a hydrazine derivative that is a colorless crystal or tablet at room temperature. It is very soluble in ethanol, slightly soluble in benzene and deuterated dimethyl sulfoxide, insoluble in acetic acid, and practically insoluble in water (HSDB 2009). Hydrazobenzene is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of hydrazobenzene are listed in the following table.

Property	Information
Molecular weight	184.2
Specific gravity	1.158 at 16°C/4°C
Melting point	131°C (decomposes)
Boiling point	293°C at 760 mm Hg
Log K_{ow}	2.94
Water solubility	221 mg/L at 25°C
Vapor pressure	0.00044 mm Hg at 25°C
Dissociation constant (pK_a)	-0.65

Source: HSDB 2009.

Use

Hydrazobenzene has been used primarily in the dye manufacturing industry as the precursor of the dye intermediate benzidine (HSDB 2009). It is also used as an intermediate in the manufacture of pharmaceuticals such as sulfinpyrazone and phenylbutazone, which have been used to treat gout (Roberts and Morrow 2001, HSDB 2009). Some minor direct uses of hydrazobenzene are in polymerization reactions and as an anti-sludging additive to motor oil, desucker-ing agent for tobacco plants, reductant in the reclamation of rubber, component of experimental organometallic polymers, and component in photochromic resin compositions (HSDB 2009). It is also used in the manufacture of hydrogen peroxide and has been evaluated for insecticidal activity.

Production

Production of at least 450,000 kg (992,000 lb) of hydrazobenzene was reported in 1977 (HSDB 2009). Dye-manufacturing facilities produced additional unknown quantities of hydrazobenzene as an intermediate in the production of benzidine, which is formed by the reduction of nitrobenzene to hydrazobenzene followed by the rearrangement of hydrazobenzene to benzidine (NCI 1978). Manufacturing of benzidine-based dyes ceased in 1988 (ATSDR 1990). In 2009, hydrazobenzene was produced by three manufacturers in India (SRI 2009) and was available from 26 suppliers worldwide, including 15 U.S. suppliers (ChemSources 2009). U.S. imports of hydrazobenzene were 72,100 kg (158,600 lb) in 1977 and 23,200 kg (51,000 lb) in 1982.

Exposure

The routes of potential human exposure to hydrazobenzene are inhalation, ingestion, and dermal contact. The potential for exposure to hydrazobenzene formerly was greatest in the benzidine-based-dye industry (NCI 1978, ATSDR 1990). The greatest potential for expo-

sure now is due to its use as an intermediate in the manufacture of certain pharmaceutical products. Because phenylbutazone and sulfinpyrazone can hydrolyze to hydrazobenzene, people who take these drugs to prevent gout attacks may be exposed to hydrazobenzene (ATSDR 1990). These drugs are used primarily in veterinary medicine; the extent of their current use in humans is unknown. In 2009, seven products approved by the U.S. Food and Drug Administration for use in humans contained sulfinpyrazone as an active ingredient, but all eleven pharmaceutical products containing phenylbutazone were listed as discontinued (FDA 2009).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, small quantities of hydrazobenzene have been released to air, surface water, and landfills. Annual releases of hydrazobenzene since 1998 have not exceeded 12 lb except in 2001, when 260 lb was released to an off-site nonhazardous-waste landfill. In 2007, one U.S. facility released 10 lb of hydrazobenzene to a hazardous-waste landfill (TRI 2009). Hydrazobenzene can exist in both particulate and vapor phases in the atmosphere. In the vapor phase, it degrades by reaction with photochemically produced hydroxyl radicals, with a half-life of 5 hours. In the particle phase, it can be removed by wet and dry deposition. If released to soil or water, it is expected to bind to soil, suspended solids, and sediment and have low soil mobility. It is not expected to volatilize readily from water or soil or to bioaccumulate to a large extent in aquatic organisms. Degradation of hydrazobenzene is reversible; hydrazobenzene undergoes oxidation to azobenzene under aerobic solutions, catalyzed by common environmental cations such as copper(II) and iron(III). In a municipal sewage effluent, the half-life for the decomposition of 100 µg of hydrazobenzene per liter was 60 minutes if oxygen was removed from the sewage, but only 15 minutes if the oxygen was not removed (ATSDR 1990). Hydrazobenzene was detected in 1.2% of 1,205 effluent samples collected from wastewater treatment plants in a national survey, at a median concentration of 10 µg/L (HSDB 2009). Hydrazobenzene was also found in drinking water at a concentration of 1 µg/L and was detected in fish taken from the Great Lakes.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 977 U.S. workers, including 154 women, potentially were exposed to hydrazobenzene (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.036 µg/L; based on fish or shellfish consumption only = 0.20 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of hydrazobenzene = U109.

Listed as a hazardous constituent of waste.

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Ionizing Radiation

Introduction

Ionizing radiation is electromagnetic radiation that has sufficient energy to remove electrons from atoms. Ionization results in the production of negatively charged free electrons and positively charged ionized atoms. Ionizing radiation can be classified into two categories: photons (X-radiation and gamma radiation) and particles (alpha and beta particles and neutrons). Five types or sources of ionizing radiation are listed in the Report on Carcinogens as *known to be human carcinogens*, in four separate listings:

- X-radiation and gamma radiation (included in one listing) were first listed in the *Eleventh Report on Carcinogens* (2004).
- Neutrons were first listed in the *Eleventh Report on Carcinogens* (2004).
- Radon and its isotopic forms radon-220 and radon-222, which emit primarily alpha particles, were first listed in the *Seventh Annual Report on Carcinogens* (1994).
- Thorium dioxide, which decays by emission of alpha particles, was first listed in the *Second Annual Report on Carcinogens* (1981).

Below are the profiles for the four ionizing radiation listings, covering carcinogenicity, properties, use, sources or production, exposure, and references cited separately for each profile, followed by a list of regulations and guidelines applicable to all five types or sources of ionizing radiation listed.

X-Radiation and Gamma Radiation

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as X-rays, gamma rays, and γ radiation

Carcinogenicity

X-radiation and gamma radiation are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies of radiation exposure provide a consistent body of evidence for the carcinogenicity of X-radiation and gamma radiation in humans. Exposure to X-radiation and gamma radiation is most strongly associated with leukemia and cancer of the thyroid, breast, and lung; associations have been reported at absorbed doses of less than 0.2 Gy (see Properties, below, for explanation of radiation dose measurement). The risk of developing these cancers, however, depends to some extent on age at exposure. Childhood exposure is mainly responsible for increased leukemia and thyroid-cancer risks, and reproductive-age exposure for increased breast-cancer risk. In addition, some evidence suggests that lung-cancer risk may be most strongly related to exposure later in life. Associations between radiation exposure and cancer of the salivary glands, stomach, colon, urinary bladder, ovary, central nervous system, and skin also have been reported, usually at higher doses of radiation (1 Gy) (Kleinerman *et al.* 1995, Ron 1998, Ron *et al.* 1999, Brenner *et al.* 2000, Garwicz *et al.* 2000, Lichter *et al.* 2000, Sont *et al.* 2001, Yeh *et al.* 2001, Bhatia *et al.* 2002).

The first large study of sarcoma (using the U.S. Surveillance, Epidemiology, and End Results cancer registry) (Yap *et al.* 2002) added angiosarcoma to the list of radiation-induced cancers occurring within the field of radiation at high therapeutic doses. Two studies, one of workers at a Russian nuclear bomb and fuel reprocessing plant (Gilbert *et al.* 2000) and one of Japanese atomic-bomb survivors (Cologne *et al.* 1999), suggested that radiation exposure could cause liver cancer at doses above 100 mSv (in the worker population especially with concurrent exposure to radionuclides). Among the atomic-bomb survivors, the liver-cancer risk increased linearly with increasing radiation dose. A study of children medically exposed to radiation (other than for cancer treatment) provided some evidence that radiation exposure during childhood may increase the incidence of lymphoma and melanoma.

Studies on Mechanisms of Carcinogenesis

X-radiation and gamma radiation have been shown to cause a broad spectrum of genetic damage, including gene mutations, minisatellite mutations, micronucleus formation, chromosomal aberrations, ploidy changes, DNA strand breaks, and chromosomal instability. Genetic damage by X-radiation or gamma radiation has been observed in humans exposed accidentally, occupationally, or environmentally, in experimental animals exposed *in vivo*, and in cultured human and other mammalian cells. X-radiation and gamma radiation cause genetic damage in somatic cells and transmissible mutations in mammalian germ cells. The DNA molecule may be damaged directly, by interaction with ionizing radiation, or indirectly, by interaction with reactive products of the degradation of water by ionizing radiation (i.e., free electrons, hydrogen free radicals, or hydroxyl radicals) (IARC 2000, NTP 2003). The observed genetic damage is primarily the result of errors in DNA repair, but may also arise from errors in replication of damaged DNA. Epigenetic mechanisms that alter the action of genes also may be involved in radiation-induced carcinogenesis. Proposed mechanisms for delayed or indirect radiation-induced genetic damage include genomic instability, induction of mutations by irradiation of the cytoplasm of the cell, and “bystander effects,” in which genetic damage is induced in cells that were not directly exposed to ionizing radiation, apparently through cell signaling pathways.

Cancer Studies in Experimental Animals

X-radiation and gamma radiation are clearly carcinogenic in all species of experimental animals tested (mice, rats, and monkeys for X-radiation and mice, rats, rabbits, and dogs for gamma radiation). Among these species, radiation-induced tumors have been observed in at least 17 different tissue sites, including sites at which tumors were observed in humans (i.e., leukemia, thyroid gland, breast, and lung) (IARC 2000). Susceptibility to induction of tumors depends on tissue site, species, strain, age, and sex. Early prenatal exposure does not appear to cause cancer, but exposure at later stages of prenatal development has been reported to do so. It has been suggested that radiation exposure of mice before mating increases the susceptibility of their offspring to cancer; however, study results are conflicting.

Properties

As forms of electromagnetic radiation, X-rays and gamma rays are packets of energy (photons) having neither charge nor mass. They have essentially the same properties, but differ in origin. X-rays are emitted from processes outside the nucleus (e.g., bombardment of heavy atoms by fast-moving electrons), whereas gamma rays originate inside the nucleus (during the decay of radioactive atoms). The energy of ionizing radiation is expressed in electronvolts, a unit equal to the energy acquired by an electron when it passes through a potential difference of 1 volt in a vacuum; $1 \text{ eV} = 1.6 \times 10^{-19} \text{ J}$ (IARC 2000).

The energy of X-rays typically ranges from 5 to 100 keV. Lower in energy than gamma rays, X-rays are less penetrating; a few millimeters of lead can stop medical X-rays. The energy distribution of X-radiation is continuous, with a maximum at an energy about one third that of the most energetic electron. The energy of gamma rays resulting from radioactive decay typically ranges from 10 keV to 3 MeV. Gamma rays often accompany the emission of alpha or beta particles from a nucleus. Because of scattering and absorption within the radioactive source and the encapsulating material, the emitted photons have a relatively narrow energy spectrum (i.e., are monoenergetic). Gamma rays are very penetrating; they can easily pass through the human body, but they can also be absorbed by tissue. Several feet of concrete or a few inches of lead are required to stop the more energetic gamma rays (BEIR V 1990).

As photons interact with matter, their energy distribution is altered in a complex manner as a result of energy transfer. The amount of energy deposited by ionizing radiation per unit of path length in irradiated material is called the “linear energy transfer” (LET), expressed in units of energy per unit length (e.g., kiloelectronvolts per micrometer). X-rays and gamma rays are considered low-LET radiation. In tissue, they transfer their energy primarily to electrons. Compared with high-LET radiation (such as neutrons and alpha particles), low-LET radiation tends to follow more tortuous paths in matter, with more widely dispersed energy deposition.

Use

X-rays, gamma rays, and materials and processes that emit X-rays and gamma rays are used in medicine, the nuclear power industry, the military, scientific research, industry, and various consumer products.

Medical use of ionizing radiation in both diagnosis and therapy has been widespread since the discovery of X-rays by Wilhelm Conrad Roentgen in 1895, and radioactive sources have been used in radiotherapy since 1898. Advances in the latter half of the 20th century increased the use of medical radiation, and some newer techniques, particularly radiotherapy, computed tomography, positron emission tomography, and interventional radiation involving fluoroscopy, use higher radiation doses than do standard diagnostic X-rays. Radiation therapy may involve use of external beams of radiation, typi-

cally high-energy X-rays (4 to 50 MeV) and cobalt-60 gamma rays (UNSCEAR 2000).

Military uses of materials and processes that emit X-radiation and gamma radiation include the production of materials for nuclear weapons and the testing and use of nuclear weapons. In 1945, atomic bombs were detonated over Hiroshima and Nagasaki, Japan. Between 1945 and 1980, nuclear weapons were tested in the atmosphere of the Northern Hemisphere; during the most intense period of testing, from 1952 to 1962, about 520 tests were carried out (IARC 2000).

Several industrial processes use ionizing radiation. Industrial radiography uses gamma radiation to examine welded joints in structures. In the oil industry, gamma radiation or neutron sources are used to determine the geological structures in a bore hole (a process called “well logging”) (NCRP 1989). Ionizing radiation is also used to sterilize products and irradiate foods (to kill bacteria and parasites) (IARC 2000).

Ionization-type smoke detectors contain americium-241, which emits gamma radiation and alpha particles. In the past, detectors with up to 3.7 MBq of americium-241 were used in commercial and industrial facilities, but current smoke detectors contain less than 40 kBq (IARC 2000). Television sets emit low-energy X-rays through a process by which electrons are accelerated and bombard the screen (ATSDR 1999). Other products containing sources of ionizing radiation (of unspecified types) include radioluminescent clocks and watches, gaseous tritium light devices (e.g., self-luminous signs), thoriated gas lamp and lantern mantles, radioactive attachments to lightning conductors, static elimination devices, fluorescent lamp starters, porcelain teeth, gemstones activated by neutrons, and thoriated tungsten welding rods. For all of these products, the maximum allowable radioactivity is restricted, and radiation from these products contributes little to overall exposure of the population (IARC 2000).

Sources

The most important sources of X-radiation and gamma radiation include natural sources, medical uses, atmospheric nuclear weapons tests, nuclear accidents, and nuclear power generation. Ionizing radiation is present naturally in the environment from cosmic and terrestrial sources. Cosmic radiation is a minor source of exposure to X-radiation and gamma radiation; most natural exposure is from terrestrial sources. Soil contains radioactivity derived from the rock from which it originated. However, the majority of radioactive elements are chemically bound in the earth's crust and are not a source of radiation exposure unless released through natural forces (e.g., earthquake or volcanic activity) or human activities (e.g., mining or construction). Generally, only the upper 25 cm of the earth's crust is considered a significant source of gamma radiation. Indoor sources of gamma radiation may be more important than outdoor sources if earth materials (stone, masonry) were used in construction (IARC 2000).

Exposure

Biological damage by ionizing radiation is related to dose and dose rate, which may affect the probability that cancer will occur (IARC 2000). Radiation dose is a measure of the amount of energy deposited per unit mass of tissue and may be expressed as the absorbed dose, equivalent dose, or effective dose. The standard unit for absorbed dose is the gray, which is equal to 1 J/kg of deposited energy. The absorbed dose formerly was expressed in rads (1 Gy = 100 rads). The biological effect of high-LET radiation is greater than that of low-LET radiation at the same absorbed dose; therefore, a dose measurement independent of radiation type was derived to reflect the biological effectiveness of radiation in causing tissue damage. The “equivalent

dose” (also known as the “dose equivalent”) is obtained by multiplying the absorbed dose by a radiation weighting factor (W_R ; formerly called the “quality factor”). Radiation weighting factors are assigned to radiation of different types and energies by the International Commission on Radiological Protection based on their biological effects relative to those of a reference radiation, typically X-rays or gamma rays; W_R ranges from 1 (for low-LET radiation) to 20 (for high-LET radiation). The standard unit for the equivalent dose is the sievert. The equivalent dose formerly was expressed in rems (1 Sv = 100 rem). Because $W_R = 1$ for both X-rays and gamma rays, the absorbed and equivalent doses are the same (ICRP 1991). Another measurement, the “effective dose,” takes into account the fact that the same equivalent dose of radiation causes more significant biological damage to some organs and tissues than to others. Tissue weighting factors (W_T) are assigned to the various organs and tissue types, and the effective dose is calculated as the sum of the tissue-weighted equivalent doses in all exposed tissues and organs in an individual. The effective dose is expressed in sieverts. The collective radiation dose received by a given population may be expressed as the “collective equivalent dose” (also known as the “collective dose equivalent”), which is the sum of the equivalent doses received by all members of the population, or as the “collective effective dose,” which is the sum of the effective doses received by all members of the population. Both the collective equivalent dose and the collective effective dose are expressed in person-sieverts.

All individuals are exposed to ionizing radiation from a variety of natural and anthropogenic sources. Of the general population's exposure to all types of ionizing radiation (not just X-radiation and gamma radiation), natural sources contribute over 80%; radon gas and its decay products account for about two thirds of natural exposure, and the other third is from cosmic radiation, terrestrial radiation, and internally deposited radionuclides. The remaining exposure to ionizing radiation is from anthropogenic sources, such as medical procedures (15%), consumer products (3%), and other sources (totaling less than 1%), which include occupational exposure, nuclear fallout, and the nuclear fuel cycle (BEIR V 1990). In 2000, the worldwide estimated average annual per-capita effective doses of ionizing radiation (of any type) were 2.4 mSv (range = 1 to 20 mSv) for natural background exposure and 0.4 mSv (range = 0.04 to 1 mSv) for medical diagnostic exposure. However, in countries with the highest level of health care (< 1,000 population per physician), the average radiation dose from medical X-rays was estimated at 1.2 mSv, or about half the average natural exposure level. Estimated average annual effective doses from past atmospheric nuclear testing, the nuclear power plant accident in Chernobyl, Ukraine, and nuclear power production were only 0.005 mSv, 0.002 mSv, and 0.0002 mSv, respectively (UNSCEAR 2000).

Radiation exposure from medical uses is much more variable than that from natural background radiation (even though the latter varies considerably among locations) because of marked differences in the quality of medical care among cultures. In the more developed nations, higher percentages of the population receive regular medical care, and thus exposures from diagnostic radiology and radiotherapy tend to be higher than in developing nations. Exposure to diagnostic X-rays varies but generally is low; plain film examinations of the chest and extremities involve relatively low effective doses (0.05 to 0.4 mSv), whereas examinations of the abdomen and lumbar spine or pelvis may result in higher effective doses (1 to 3 mSv). Radiation therapy uses much larger doses of radiation than do diagnostic procedures. For example, treatment for leukemia usually involves irradiation of the total bone marrow, with absorbed doses of about 10 to 20 Gy delivered in several fractions (UNSCEAR 2000).

Excluding uranium miners and other workers whose radiation exposure is individually monitored, about 5 million people worldwide are occupationally exposed to natural sources of ionizing radiation (of any type) at levels above the natural background. About 75% are coal miners (whose estimated average annual effective dose is 1 to 2 mSv), about 13% are other underground miners (whose estimated average annual dose is 1 to 10 mSv), and about 5% are airline crews (who receive an estimated average annual dose of up to 3 mSv). Miners are exposed mainly through inhalation of radon; thus, they are exposed primarily to alpha particles, but also to gamma radiation. Airline crews are exposed primarily to gamma radiation, but also to neutrons (UNSCEAR 1993, IARC 2000).

Medical workers may be exposed to many different types of radionuclides and radiation. In the early 20th century, before radiation hazards were recognized, radiologists were exposed to high doses of X-radiation (IARC 2000). The first dose limit established for radiologists, in 1902, allowed exposure of approximately 30 Gy per year (Mabuchi 2002), but doses are now much lower (< 1 mSv) (Mostafa *et al.* 2002). Other settings with potential for occupational exposure to X-radiation or gamma radiation include the nuclear industry, military activities, research laboratories, and various industries where radioactive materials or radiography are used (IARC 2000).

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Neutrons

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

Carcinogenicity

Neutrons are *known to be a human carcinogen* based on studies on their mechanisms of carcinogenesis, which demonstrated that neutrons cause genetic damage in humans similar to that caused by X-radiation and gamma radiation, induce chromosomal aberrations in humans, and produce gamma radiation when they interact with biological materials. In addition, there is sufficient evidence of carcinogenicity from studies in experimental animals.

Studies on Mechanisms of Carcinogenesis

Neutrons cause a broad spectrum of genetic damage similar to that caused by X-radiation and gamma radiation, including gene mutations, micronucleus formation, sister chromatid exchange, chromosomal aberrations, DNA strand breaks, and chromosomal instability. Genetic damage by neutron radiation has been observed in humans exposed occupationally or medically, in experimental animals exposed *in vivo*, and in cultured human and other mammalian cells. Studies of humans exposed to neutron radiation showed that induced chromosomal aberrations persisted for decades, and some cell-culture studies showed genomic instability in the progeny of irradiated human cells (IARC 2000, Littlefield *et al.* 2000). Many cell-culture studies have consistently demonstrated that neutron radiation causes chromosomal aberrations in human peripheral-blood lymphocytes more effectively than does gamma radiation (IARC 2000). Reciprocal translocations in male germ cells were observed in rhesus monkeys.

Although the genetic damage caused by neutron radiation is qualitatively similar to that caused by X-radiation and gamma radiation, it differs quantitatively. Low-energy neutrons, such as fission neutrons (those resulting from the splitting of atomic nuclei), are significantly more potent carcinogens in experimental animals than is low-LET radiation, such as X-rays or gamma rays. Types of ionizing radiation with differing LET differ in their effects on biological tissue; however, the observed differences are not sufficient to indicate that the biological effects of high-LET (i.e., neutrons) and low-LET radiation differ qualitatively. In general, neutron radiation induces chromosomal aberrations, mutations, and DNA damage more efficiently than does low-LET radiation. DNA lesions caused by neutron radiation are more severe and are repaired less efficiently, and neutron radiation induces higher proportions of complex chromosomal aberrations (Pogozelski *et al.* 1999, Boei *et al.* 2001, Brenner *et al.* 2001). However, there is no conclusive evidence of a signature alteration that might distinguish tumors induced by high-LET radiation from those induced by low-LET radiation.

Cancer Studies in Experimental Animals

Neutrons are clearly carcinogenic in all species of experimental animals tested, including mice, rats, rabbits, dogs, and monkeys. Among

these species, radiation-induced tumors have been observed in at least 20 different tissue sites, including sites at which tumors were observed in humans (i.e., leukemia, thyroid gland, breast, and lung) (IARC 2000). Susceptibility to induction of tumors depends on tissue site, species, strain, age, and sex.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to neutron radiation.

Properties

Neutrons are electrically neutral particles found in the nuclei of atoms and are similar in mass to protons, which also are present in the nucleus. Because neutrons have no electrical charge, they do not interact with atomic electrons, but they do interact with atomic nuclei. The nuclear force, which holds particles together in the nucleus and leads to these interactions, has a very short range, which means that a neutron must pass close to a nucleus for an interaction to take place. These atomic interactions generate protons, alpha particles, and other nuclear fragments, along with gamma radiation. Because of the small size of the nucleus in relation to the atom as a whole, neutrons have a low probability of interaction and thus are very penetrating. Depending on their energy, they can travel up to several tens of centimeters through tissue (IARC 2000). Water (in nuclear reactors) and thick concrete (in particle accelerators) typically are used as shielding, because interactions with hydrogen nuclei (single protons, which are similar in mass to neutrons) are most effective at reducing neutron energy.

Neutrons cause ionization in biological tissue through elastic collisions with the nuclei of atoms composing tissue molecules. In collisions of neutrons with the hydrogen nuclei of water (the major component of the human body), the recoiling hydrogen nuclei (charged protons) are the source of ionizing events. Elastic collisions of high-energy neutrons (over 50 MeV) with larger nuclei, such as those of carbon, oxygen, nitrogen, and calcium atoms, result in violent interactions that produce many low-energy charged particles. Because the masses of protons and the other recoiling nuclei are much greater than the mass of an electron, neutron radiation generates a dense ion path, causing more damage to tissue than a similar dose of X-rays or gamma rays. Neutrons therefore are considered high-LET radiation. With each collision, about half of the neutron's energy is given to the proton. As the neutron loses energy, it slows down until it is absorbed into the nucleus of an atom, which often makes the absorbing atom radioactive (IARC 2000, Busby 2001).

Use

Neutron radiation is used less than other types of radiation in industry, medicine, and research. Neutron radiation has not been used widely for medical purposes, because it has not shown clear therapeutic benefits, compared with conventional radiotherapy. However, there has been renewed interest in fast-neutron therapy for some cancers (Britten *et al.* 2001, Forman *et al.* 2002). Current medical uses of neutrons include external beam therapy, boron neutron capture therapy, and production of radioisotopes used in medical diagnosis and cancer therapy. Neutron sources are used in oil-well logging and to induce chain reactions in nuclear reactors. Other uses include neutron activation analysis and radiography (for determination of the elemental composition and moisture content of various materials), sterilization of materials, radiometric dating of rocks, and scientific and engineering research (ATSDR 1999, IARC 2000, Lowy *et al.* 2001).

Sources

The atomic nucleus is the source of all neutron radiation, but neutrons can be released in several ways. Because the nuclear constituents are tightly bound, several million electronvolts are required to free a neutron from most nuclei (IARC 2000). Sources of neutron radiation include the following: the interaction of high-energy cosmic rays with the earth's atmosphere, nuclear fusion or fission of atomic nuclei in nuclear reactors or atomic explosions, collision of charged particles with a lithium or beryllium target, and spontaneous fission of californium-252 (ATSDR 1999, IARC 2000).

Exposure

The worldwide population is exposed to neutron radiation from natural sources. Populations with additional exposure include cancer patients receiving radiation therapy, nuclear-industry workers, survivors of atomic bomb blasts, and airline crews and passengers. In almost all cases, individuals are exposed to mixed radiation fields in which neutrons are a minor component. Exceptions are patients receiving neutron radiotherapy and airline crews and passengers, who may receive up to 60% of their equivalent dose from neutron radiation.

The general population is exposed to neutrons primarily from cosmic radiation originating from outer space; however, only the most energetic particles produce effects at ground level (IARC 2000). A small portion of cosmic radiation originates from the sun. The amount increases during periods of increased sunspot and solar-flare activity, which run in approximately 11-year cycles; the largest event to date occurred in February 1956, when neutron counts at ground level rose 3,600% above normal background levels (ATSDR 1999, IARC 2000). The average dose of neutron radiation from cosmic radiation increases at higher altitudes; the dose in Denver, Colorado, at an altitude of 1,600 m (1 mi) is about twice that received at sea level (IARC 2000). The estimated annual effective dose of neutron radiation at sea level at 50° latitude is 80 μ Sv (UNSCEAR 2000). The atomic bombs exploded over Hiroshima and Nagasaki, Japan, in 1945 released low levels of neutron radiation to the environment (an estimated 1% to 2% of the total dose of ionizing radiation from the bombs was from neutrons) (IARC 2000).

Airline crews and passengers are exposed to varying doses of neutron radiation, depending on flight route, aircraft type, and number of hours in flight. Annual average equivalent doses for airline crews have been estimated to range from 0.6 to 3.6 mSv. Collective equivalent doses of neutron radiation received by passengers have been estimated based on air travel rates. For example, in 1985, total time in flight was estimated as 3×10^9 passenger hours; based on an estimated average equivalent dose rate of 1.6 μ Sv per hour, the annual collective equivalent dose was 5,040 person-Sv. By 1997, time in flight had grown to 4.3×10^9 passenger hours, resulting in an annual collective equivalent dose of 7,200 person-Sv (IARC 2000).

Occupational exposure to neutron radiation occurs to a limited extent in the nuclear industry; however, these workers are exposed primarily to gamma radiation. A study using data from 1977 to 1984 estimated the average annual effective dose of neutron radiation among U.S. radiation workers employed by Department of Energy contractors, nuclear power stations, and the U.S. Navy to be 1.8 mSv and the collective effective dose to be 67.5 person-Sv (IARC 2000). In another U.S. study, the average equivalent dose of neutron radiation to nuclear power plant workers was 5.6 mSv, and the collective equivalent dose was 0.038 person-Sv (NCRP 1989). Overall, less than 3% of the total annual effective radiation dose to nuclear industry workers in the United Kingdom from 1946 to 1988 was due to neutrons (Carpenter *et al.* 1994). Workers involved in the production of nuclear weapons may be exposed to low levels of neutron radiation. In

1979, 24,787 U.S. workers in DOE facilities (80% of whom performed defense-related work) were monitored for exposure to neutron radiation; only 326 (1.4%) received annual equivalent doses higher than 5 mSv (IARC 2000). Oil-field workers may be exposed to low doses of neutron radiation during well logging; the average annual equivalent dose was estimated at 1 to 2 mSv (Fujimoto *et al.* 1985).

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Radon

CAS No. 10043-92-2

Known to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)

Also known as Rn

Carcinogenicity

Radon and its isotopic forms radon-222 and radon-220 are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Increased incidences of lung cancer have been reported in numerous epidemiological studies of groups occupationally exposed to radon at high doses (IARC 1988, ATSDR 1990). Evidence supporting this listing was based principally on earlier mortality studies of underground mine workers. In one of the largest prospective studies, two cohorts totaling 3,400 white and 780 Native American uranium miners and millers in Colorado were followed from 1950 to 1977. Among white males, the risk of lung cancer was significantly increased 4- to 6-fold, depending on the comparison population used; the risk of cancer at other tissue sites was not increased. The risk of lung cancer increased significantly with increasing cumulative radon exposure, supporting

a causal relationship. Other prospective and retrospective cohort and case-control studies of uranium miners, together with studies of miners of iron ore (hematite), other metals, and fluorite, conducted between the 1960s and 1980s consistently found that lung-cancer risk increased with increasing cumulative exposure (despite some methodological limitations in exposure estimation, particularly in retrospective studies). In some cohorts, radon exposure was also associated with increased risks of tracheal and bronchial cancer. Smaller case-control studies also suggested an association between lung-cancer risk and indoor residential exposure to radon, mainly from ground sources (IARC 1988).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of radon from studies in experimental animals. In male rats, inhalation exposure to radon caused lung cancer (adenoma, adenocarcinoma, alveolar/bronchiolar carcinoma, and squamous-cell carcinoma), and incidences of respiratory-tract tumors were increased further by exposure to both radon and cigarette smoke or cerium hydroxide particles. In dogs of both sexes, inhalation exposure to a combination of radon, radon decay products, and uranium ore dust caused lung cancer (epidermoid carcinoma, alveolar/bronchiolar carcinoma, and fibrosarcoma) and nasal cancer (carcinoma). A review of studies in rats exposed to radon by inhalation also reported increased incidences of tumors of the upper lip and urinary tract. In a study in hamsters, only three animals developed features of squamous-cell carcinoma after 16 to 17 months of exposure to radon decay products or radon decay products and uranium ore dust. The International Agency for Research on Cancer (IARC 1988, 2001) concluded that there was sufficient evidence for the carcinogenicity of radon and its decay products in experimental animals.

Properties

Radon is a naturally occurring element and is the heaviest of the noble (chemically inert) gases. Of radon's 20 known isotopes, only three occur naturally, all of which are radioactive. Radon-222, produced by the decay of radium-226, is the most common and most stable isotope, with a half-life of 3.82 days. Radon-220, or thoron, is produced in the decay series of thorium-232 and has a half-life of 55 seconds. Radon-219, or actinon, is produced in the decay series of uranium-235 and has a half-life of 4 seconds (CEE 2003). Radon is colorless, tasteless, and odorless and is fairly soluble in water and organic solvents. It spontaneously decays into a series of short-lived radioisotopes of heavy metals (polonium, lead, and bismuth) commonly referred to as "radon daughters" or "radon progeny." Decay of radon and of its decay products results in the release of alpha particles and gamma radiation. When radon is released into air, its solid decay products readily attach to airborne dust (IARC 1988, ATSDR 1990). Physical and chemical properties of radon are listed in the following table.

Property	Information
Density	9.73 g/L at 0°C
Melting point	-71°C
Boiling point	-61.8°C
Vapor pressure	395.2 mm Hg at -71°C

Source: ATSDR 1990.

Use

Radon is used primarily for research; it has no significant industrial uses. It is used to initiate and influence chemical reactions, as a surface label in the study of surface reactions, in combination with beryllium or other light materials as a source of neutrons, in petroleum and uranium exploration, and in earthquake prediction (ATSDR 1990,

HSDB 2009). In U.S. locations with naturally high levels of radon in water or air, exposure to radon has been used since the early 1900s to purportedly treat a wide variety of diseases, such as skin disorders, hardening of the arteries, ulcers, allergies, arthritis, and high blood pressure. Radon also was used to treat malignant tumors; it was encapsulated in gold “seeds,” which were implanted at the tumor site (ATSDR 1990).

Production

Radon is produced in nature by radioactive decay of radium. Radon-222 is produced by decay of radium-226, a long-lived product of the uranium-238 decay series. Radon-220 is produced by decay of radium-224 in the thorium-232 decay series, and radon-219 by decay of radium-223 in the uranium-235 decay series. It is estimated that every square mile of soil to a depth of 6 inches contains about 1 g of radon. Radon is released from soil into air and groundwater, and thus occurs at low concentrations throughout the environment. Radon concentrations are highest in areas with uranium and thorium ore deposits and granite formations (ATSDR 1990). Radon-222 makes by far the largest contribution to environmental radon concentrations and is the isotope on which exposure estimates have been based (IARC 2001).

Radon was produced commercially for use in radiation therapy, but for the most part has been replaced by other radionuclides. Some radon is produced in research laboratories and universities for use in experimental studies. Radon is not imported or exported by the United States (ATSDR 1990, HSDB 2009).

Exposure

Among the general population, radon accounts for about half of the worldwide average annual background effective dose of radiation, which is 2.4 mSv (IARC 2001). Elevated radon levels have been discovered at locations in virtually every U.S. state, but levels vary considerably, even within a given location. The U.S. Environmental Protection Agency developed a generalized map of U.S. radon zones by county, based on predicted average indoor radon screening levels: Zone 1 includes counties with predicted levels above 4 pCi/L (148 Bq/m³), Zone 2 includes counties with predicted levels between 2 and 4 pCi/L, and Zone 3 includes counties with predicted levels below 2 pCi/L (74 Bq/m³) (EPA 2003a). In general, Zone 1 areas are concentrated in the northern half of the United States and the Appalachian mountains, and Zone 3 areas are concentrated in the piedmont and coast of the Southeast, Louisiana, Arkansas, Oklahoma, and Texas, and on the Northwest coast. EPA estimates that 1 in 15 homes have elevated radon levels (4 pCi/L or higher). As of 2003, radon exposure in U.S. single-family homes was thought to be a causal factor in as many as 15,000 to 22,000 lung cancer deaths per year (EPA 2003b).

The primary routes of environmental exposure to radon are inhalation and ingestion. Radon in groundwater, soil, or building materials enters working and living spaces and decays, emitting ionizing radiation. Environmental radon concentrations vary with geographical location and other factors. Average radon concentrations in U.S. groundwater are about 8.8 Bq/L in large aquifers and 28.9 Bq/L in small aquifers and wells. In the continental United States, concentrations in outdoor air range from about 4.1 to 15.2 Bq/m³, with a mean of about 8.9 Bq/m³. However, concentrations of up to 30 Bq/m³ were measured on the Colorado Plateau. Average radon levels are higher in indoor than outdoor air; indoor levels reportedly range from 55 to 157 Bq/m³ (ATSDR 1990). Emanation of radon from rock, soil, and groundwater can cause significant radon concentrations in tunnels, power stations, caves, public baths, and spas (IARC 1988).

Workers employed in uranium, hard-rock, and phosphate mining potentially are exposed to radon at high concentrations. Uranium miners generally are believed to have the highest exposures. However, the number of operating U.S. underground uranium mines decreased from 300 in 1980 to only 16 in 1984, and the number of underground uranium mine workers from 9,000 in 1979 to 448 in 1986. Concentrations of radon decay products in the air of underground mines vary. Annual geometric mean concentrations of radon decay products in U.S. uranium mines from 1976 to 1985 ranged from 800 to 2,664 Bq/m³, while concentrations in phosphate mines ranged from 888 to 8,880 Bq/m³. Radon exposure in underground mines has been greatly reduced through engineering controls. In New Mexico mines, implementation of control measures reduced radon exposure by an order of magnitude from 1967 to 1980 (ATSDR 1990).

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Thorium Dioxide

CAS No. 1314-20-1

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as thorium oxide



Carcinogenicity

Thorium dioxide is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Evidence for the carcinogenicity of thorium dioxide comes from follow-up epidemiological studies of patients who received intravascular injections of Thorotrast (thorium dioxide used as a contrast agent in medical radiology; see Use, below). A large excess of liver tumors (primarily cholangiocellular tumors and hemangiosarcoma) was observed in the Thorotrast-treated patients. Excesses of other cancer, including leukemia and bone cancer, were reported in other studies (van Kaick *et al.* 1978, da Motta *et al.* 1979, Faber 1979, Mori *et al.* 1979).

Since thorium dioxide was listed in the *Second Annual Report on Carcinogens*, additional follow-ups of the Thorotrast cohorts have been reported. These cohort studies were reviewed by the International Agency for Research on Cancer in its evaluation of *Some Internally Deposited Radionuclides* (IARC 2001). IARC reported the results of five major cohort studies (in Germany, Denmark, Japan, Portugal, and Sweden), which followed over 10,000 patients injected with Thorotrast between the 1930s and 1950s. These studies con-

firmed the findings of the earlier studies and reported relative risks of liver-cancer mortality or incidence ranging from 36 to 129. Risks were correlated with the volume of injected Thorotrast. Hemangiosarcoma, typically a very rare tumor, accounted for about one third of the tumors. The risk of leukemia, excluding chronic lymphoid leukemia, was increased 11- to 20-fold in Thorotrast-treated patients. Findings regarding mesothelioma and cancer of the extrahepatic bile duct, gallbladder, and pancreas were inconsistent across studies.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of thorium dioxide from studies in experimental animals. When administered by intravenous injection, thorium dioxide caused cancer of the blood vessels (hemangioendotheliosarcoma) or reticuloendothelial system (sarcoma) in the liver, spleen, and lung in rabbits; liver cancer (cholangiocellular carcinoma) in hamsters; and benign liver tumors (hepatocellular adenoma) in rats. Subcutaneous injection of thorium dioxide caused cancer at the injection site (fibrosarcoma) in rats and mice, and intraperitoneal injection caused cancer (sarcoma) in rats, mice, hamsters, rabbits, and guinea pigs (Wegener 1979, EPA 1981, IARC 2001).

Properties

Thorium dioxide is the oxide of the radioactive metallic element thorium, the second member of the actinide series of elements. Thorium-232 is the most common of the naturally occurring isotopes; it decays by emission of alpha particles and has a half-life of 1.4×10^{10} years (Hedrick 2000). The other two long-lived isotopes that decay by emission of alpha particles are thorium-230 (half-life of 77,000 years) and thorium-229 (half-life of 7,300 years). Decay products include radium-228, radium-224, and radon-220 (IARC 2001). Thorium dioxide has a molecular weight of 264 and occurs as a heavy, white crystalline powder with a melting point of 3,390°C (the highest of any metal oxide) and a boiling point of 4,400°C. It is insoluble in water and alkalis and slightly soluble in acids and biological fluids. Thorium dioxide is incandescent when heated. It is available in the United States in stocks of various particle sizes with purities ranging from 99.5% to 99.99%. The X-ray contrast medium Thorotrast is a 25% colloidal thorium dioxide suspension in aqueous dextrin (IARC 2001, Clark *et al.* 2006, HSDB 2009). Thorotrast was formerly a registered trademark of the Heyden Chemical Corporation.

Use

Thorium was discovered in 1828, and its radioactivity was discovered in 1898. In the early 1900s, the only commercial use for thorium was in gas lamp mantles. Although demand for gas mantles declined with the advent of electric lights, mantle manufacturing still accounted for 92% of thorium's non-fuel use as late as 1950 (Hedrick 2000). The use of thorium in the United States has decreased substantially because of concerns over its naturally occurring radioactivity (Hedrick 2002). Principal uses for thorium dioxide are in high-temperature ceramics, gas mantles, nuclear fuel, flame spraying, crucibles, medicines, non-silica optical glass, and thoriated tungsten filaments, and as a catalyst. It has also been used as a diagnostic aid (radiopaque medium) in feline medication (HSDB 2009).

Thorotrast was used as a contrast agent in medical radiology. It was used extensively as an intravascular contrast agent for cerebral and limb angiography in Europe, the United States, and Japan. It was also injected directly into the nasal cavity, paranasal sinus, spleen, brain, and other sites. Thorotrast treatment led to deposition of thorium and its decay products in body tissues and organs, especially reticuloendothelial tissue and bone, which resulted in continuous lifelong alpha-particle irradiation (BEIR IV 1988). Use of Thorotrast was dis-

continued in the 1950s, when harmful latent effects were observed (Grampa 1971, IARC 2001).

Production

Thorium occurs in several minerals, including monazite, thorite, huttonite, and thorumite. Most thorium production occurs from mining of monazite as a by-product from heavy-mineral sands mined for titanium and zirconium minerals. Between 1987 and 1994, only one U.S. company produced monazite, all of which was exported. U.S. production of thorium-bearing monazite ended in the United States in 1994; since then, all U.S. production of thorium-containing products has relied on imports and existing industry and government stocks. About seven U.S. companies continue to process or fabricate various forms of thorium for non-energy uses such as described above (Hedrick 2002). In 2009, thorium dioxide was available from 12 U.S. suppliers (ChemSources 2009). From 1983 to 1987, annual U.S. imports of thorium dioxide equivalent ranged from 19.7 metric tons (43,000 lb) to 69.3 metric tons (153,000 lb) (ATSDR 1990). From 1996 to 2002, imports of thorium compounds, expressed as thorium dioxide equivalent, declined from 26,400 kg (58,200 lb) to 480 kg (1,060 lb) (Hedrick 2000, 2002). U.S. exports of thorium metal waste and scrap (thorium dioxide equivalent) from 1983 to 1987 ranged from 1.0 metric tons (2,200 lb) to 20.4 metric tons (45,000 lb) (ATSDR 1990). Between 1996 and 2002, exports of thorium compounds (thorium dioxide equivalent) ranged from a low of 58 kg (128 lb) in 1996 to a high of 5,390 kg (11,900 lb) in 2001 (Hedrick 2000, 2002). No more recent data on U.S. imports or exports were found.

Exposure

The primary routes of potential human exposure to thorium dioxide are inhalation, intravenous injection, ingestion, and dermal contact. Based on the amount of Thorotrast produced, more than 2.5 million people worldwide were exposed to thorium dioxide between 1930 and 1950 (IARC 2001). The injection dosages ranged from 2 to 70 mL of Thorotrast solution, depending on the area to be X-rayed (Sara-goca *et al.* 1972). Once injected, Thorotrast is not cleared from the body, resulting in lifelong exposure (BEIR IV 1988).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of thorium dioxide declined from 679,129 lb in 1988 to 42,000 lb in 1993. In 1995 and 1996, 1 lb of thorium dioxide was released, and no releases were reported from 1997 to 2007 (TRI 2009). Although thorium is widespread in the environment from both natural and anthropogenic sources, concentrations in air, soil, drinking water, and foods are very low. Very few studies have investigated daily intakes of thorium in the general population; however, estimated total daily intakes of thorium-230 and thorium-232 in air, food, and water ranged from approximately 0.02 to 0.17 pCi. Higher exposures could occur among people living near hazardous-waste sites or mining areas that contain thorium (ATSDR 1990).

Occupational exposure to thorium may occur in the mining, milling, and processing of uranium, tin, rare-earth metals, and phosphate and in gas mantle manufacturing and other thorium-processing industries (ATSDR 1990, IARC 2001). Exposure could also have occurred during the formulation, packaging, preparation, or administration of thorium dioxide as a pharmaceutical.

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Ionizing Radiation

Regulations

Department of Energy (DOE)

A comprehensive set of protection standards and program requirements has been developed for protecting individuals from ionizing radiation resulting from the conduct of DOE activities.

Radiation Dose Limits

Annual occupational dose limits for adults (the more limiting of the following): Total effective dose = 5 rem (0.05 Sv); sum of the equivalent dose to the whole body for external exposures and the committed equivalent dose to any organ or tissue other than the skin or the lens of the eye = 50 rem (0.5 Sv); eye-lens dose equivalent = 15 rem (0.15 Sv); sum of the equivalent dose to the skin or to any extremity for external exposures and the committed equivalent dose to the skin or to any extremity = 50 rem (0.5 Sv).

Dose equivalent to an embryo or fetus due to the occupational exposure of a declared pregnant woman: Shall not exceed 0.5 rem (5 mSv) during the entire pregnancy.

Annual total effective dose equivalent for individual members of the public: Shall not exceed 0.1 rem (1 mSv).

Department of Transportation (DOT)

Rules have been set governing the marking, labeling, packaging, handling, and transportation of radioactive materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Radionuclides are listed as hazardous air pollutants.

Emissions of radionuclides, other than radon, to the air shall not exceed those amounts that would cause any member of the public to receive in a year an effective dose \geq 10 mrem (0.1 mSv).

Emissions of radon-222 from an underground uranium mine shall not exceed the amount that would cause a member of the public to receive in a year an effective dose $>$ 10 mrem (0.1 mSv).

No source at a DOE facility shall emit into the air more than 20 pCi/m² per sec of radon-222 as an average for the entire source.

Each stack used in the generation of phosphogypsum shall not emit more than 20 pCi/m²-sec (1.9 pCi/ft²-sec) of radon-222 into the air.

Emissions to the ambient air from an existing uranium mill tailings pile shall not exceed 20 pCi/m²-sec (1.9 pCi/ft²-sec) of radon-222.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ): range for 758 radionuclides = 0.001 to 1,000 Ci; for radon-220 and radon-222 = 0.1 Ci.

Thorium dioxide is a listed substance subject to reporting requirements.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Indoor Radon Abatement Act

Sets a long-term goal that indoor air be as free from radon as the ambient air outside buildings, and authorizes funds for radon-reduction activities.

Marine Protection, Research, and Sanctuaries Act

Ocean disposal of high-level nuclear waste is prohibited, and any request for ocean disposal of low-level waste requires a permit that must be approved by both houses of Congress.

Nuclear Waste Policy Act

Numerous containment requirements have been set that will limit the total amount of radiation entering the environment from the Yucca Mountain (Nevada) nuclear waste repository site for over 10,000 years.

Disposal systems for waste shall be designed to provide a reasonable expectation that for 10,000 years after disposal, any member of the general population in the general environment shall not receive a combined annual dose of radiation greater than 15 mrem (0.15 mSv).

Regulations have been developed to limit radiation releases from disposal systems for spent nuclear fuel of high-level or transuranic nuclear waste.

Radiation Protection Programs

Environmental radiation protection standards for nuclear power operations have been established to limit human and environmental exposure to radiation.

Resource Conservation and Recovery Act

Radioactive waste mixed with various specified hazardous wastes are prohibited from land disposal.

Safe Drinking Water Act

Maximum contaminant level (MCL) = The average annual concentration of beta particle and photon radioactivity from manmade radionuclides in drinking water must not produce an annual dose equivalent to the total body or any internal organ greater than 4 mrem (0.4 mSv).

Uranium Mill Tailings Radiation Control Act

A comprehensive set of regulations have been established to guard against exposure to radon from uranium and thorium mill tailings.

Inactive uranium processing sites shall not release radon-220 or radon-222 to the air at levels exceeding 20 pCi/m² per sec.

Food and Drug Administration (FDA)

Rules have been established that govern ionizing radiation for the treatment of foods for human consumption and the production and processing of animal feed and pet food.

Performance standards have been set for ionizing-radiation-emitting diagnostic and therapeutic products and procedures and for accreditation and certification of facilities and personnel.

Rules have been established for use of radioactive drugs in research.

An approved new drug application is required for marketing thorium dioxide drugs.

Mine Safety and Health Administration

Regulations have been established to protect workers in underground metal and nonmetal mines against exposure to gamma radiation, including annual radiation surveys and an annual individual gamma radiation limit of 5 rem (0.05 Sv).

Regulations have been established to protect workers in underground metal and nonmetal mines against exposure to radon and radon daughters, including monitoring and record keeping requirements and various exposure limits.

Nuclear Regulatory Commission (NRC)

Comprehensive regulations have been developed to control the receipt, possession, use, transfer, and disposal of radioactive material in such a manner that the total dose to an individual does not exceed the Standards for Protection Against Radiation (see DOE Radiation Dose Limits, above). The regulations apply to entities licensed to receive, possess, use, transfer, or dispose of by-product, source, or special nuclear material or to operate a production or utilization facility, and to exposure associated with nuclear power plants and other uses of radioactive materials, including medical, veterinary, industrial, academic, and research.

Rules have been established for the medical use of radioactive material and the issuance of licenses authorizing use of the material.

Rules have been established for the packaging, preparing for shipping, and transporting of licensed radioactive material.

Rules have been established governing the receiving and storing of radioactive materials in geological repositories.

Occupational Safety and Health Administration (OSHA)

Comprehensive regulations have been set to limit worker exposure to ionizing radiation which include monitoring requirements, restricting access to areas with radiation, established exposure limits, and various precautionary procedures.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Effective dose = 50 mSv for a single year; = 20 mSv averaged over 5 years.
 Annual equivalent dose = 150 mSv for the lens of the eye; = 500 mSv for the skin, hands, and feet.
 Embryo-fetus exposure once the pregnancy is known: monthly equivalent dose = 0.5 mSv; dose to surface of women's abdomen for remainder of pregnancy = 2 mSv; recommended limit on intake of radionuclides = 1/20 of annual limit.
 Recommended dose limit for radon daughters = 4 working level months per year (WLM/yr).

Food and Drug Administration (FDA)

Radiation protection recommendations have been established for the protection of patients from radiation during diagnostic and therapeutic procedures.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) for radon progeny in underground mines = 1 working level month (WLM) per year; average workshift concentration = 1/12 of 1 WL (0.083 WL).
 A comprehensive set of recommended standards for occupational exposure to radon progeny in underground mines has been developed.

Iron Dextran Complex

CAS No. 9004-66-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as Infed, a registered trademark of Watson Pharma, Inc.

Carcinogenicity

Iron dextran complex is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to iron dextran by injection caused tumors at the injection site in several species of experimental animals. Cancer at the injection site (sarcoma) was observed following administration of iron dextran complex by subcutaneous injection in mice of both sexes and in male rats and by intramuscular injection in rats and rabbits of both sexes (IARC 1973, 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to iron dextran complex. There have been case reports of cancer occurring at the sites where iron dextran was thought to have been injected (IARC 1973, Greenberg 1976). Since iron dextran complex was listed in the *Second Annual Report on Carcinogens*, many epidemiological studies have evaluated the carcinogenicity of exposure to iron; however, these studies did not specifically examine exposure to iron dextran complex (Huang 2003).

Properties

Iron dextran complex is a chemical complex of iron hydroxide with dextrans, (polysaccharides that are produced by bacterial action on sugar) (IARC 1973). Iron dextran is a slightly viscous, dark reddish-brown liquid at room temperature (HSDB 2009). When used as a hematinic to treat iron-deficiency anemia in humans or animals, it is prepared as a dark-brown colloidal suspension in saline solution (IARC 1973). The veterinary product generally is more concentrated than the one intended for use in humans. Iron dextran complex is extremely soluble in water and insoluble in most organic solvents. It is unstable at higher temperatures and undergoes autoxidation between 65°C and 70°C (Akron 2009). Its shelf life is about five years.

Use

Iron dextran complex was first used in the United States in 1957. It is used for parenteral treatment of iron-deficiency anemia, but generally only in special cases, such as when oral treatment has failed. In 1960, approval to use iron dextran complex to treat iron-deficiency anemia in humans in the United States was withdrawn after studies in mice and rats demonstrated that repeated subcutaneous and intramuscular injections caused cancer at the injection site. However, in 1962, the use of iron dextran complex to treat iron-deficiency anemia in humans was reintroduced, as the risk of cancer in humans was thought to be small. Iron dextran complex is also used in veterinary medicine to treat baby pigs (IARC 1973, HSDB 2009).

Production

Iron dextran complex is produced by two manufacturers each in Europe and India and one manufacturer each in the United States and Canada (SRI 2009) and is available from six suppliers, including two in the United States (ChemSources 2009). Three products containing iron dextran complex are approved for use by the U.S. Food and Drug Administration (FDA 2009). No data on U.S. imports or exports of iron dextran were found.

Exposure

The primary routes of human exposure to iron dextran complex are intravenous or deep-intramuscular injection (IARC 1973, HSDB 2009). Iron dextran is available as an injectable product in 50-mg vials (FDA 2009). The therapeutic dose for humans is based on body weight and on hemoglobin when administered for iron-deficiency anemia and on blood loss and hematocrit when given for blood loss (RxList 2010). The usual daily dose is 1 to 5 mL (50 to 250 mg of iron) (IARC 1973). Use is advised only for patients who do not respond to oral administration of iron. Before 2000, nearly all parenterally administered iron supplements were iron dextran products; however, the use of iron dextran has since diminished, while use of other iron products and the use of injectable iron supplements as a class have increased (Baillie *et al.* 2005). From 2001 to 2003, about 30 million doses of iron supplements were administered by injection, 9.3 million of which were brand-name iron dextran products (Chertow *et al.* 2006). The physician's package insert for iron dextran includes a warning of the potential for injection-site sarcoma (RxList 2010).

Occupational exposure to iron dextran complex may occur during the production, formulation, packaging, or administration of the pharmaceutical products. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,157 workers, including 573 women, potentially were exposed to iron dextran complex (NIOSH 1990). Exposure during production may be site-limited, because only one manufacturer of iron dextran was identified in the United States in 2009 (SRI 2009).

Regulations

Food and Drug Administration (FDA)

Iron dextran complex is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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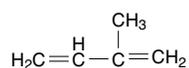
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Isoprene

CAS No. 78-79-5

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Isoprene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to isoprene by inhalation caused tumors at several different tissue sites in mice and rats. In mice of both sexes, isoprene caused blood-vessel cancer (hemangiosarcoma) and benign or malignant tumors of the Harderian gland (adenoma or carcinoma) and the lung (alveolar/bronchiolar adenoma or carcinoma). In male mice, it also caused cancer of the hematopoietic system (histiocytic sarcoma) and benign or malignant tumors of the liver (hepatocellular adenoma or carcinoma) and forestomach (squamous-cell papilloma or carcinoma). In rats of both sexes, isoprene caused benign or malignant tumors of the mammary gland (fibroadenoma or carcinoma) and kidney (renal-cell adenoma or carcinoma). In male rats, it also caused benign tumors of the testis (adenoma) (NTP 1995, Placke *et al.* 1996, Melnick and Sills 2001).

Studies on Mechanisms of Carcinogenesis

Isoprene is the 2-methyl analog of 1,3-butadiene, an industrial chemical that has been identified as a carcinogen in humans and experimental animals (Gervasi *et al.* 1985, NTP 1999a,b). The isoprene analogue isopentenyl pyrophosphate is a building block of cholesterol synthesis, and levels of exhaled isoprene correlate with cholesterol

synthesis (IARC 1994, Rieder *et al.* 2001). Isoprene and butadiene are metabolized to monoepoxide and diepoxide intermediates by liver microsomal cytochrome P450-dependent monooxygenases from several species, including humans (Gervasi *et al.* 1985, IARC 1994, NTP 1999a). These intermediates may be detoxified by hydrolysis (catalyzed by epoxide hydrolase) or conjugation with glutathione (catalyzed by glutathione S-transferase).

The diepoxide intermediates of isoprene and butadiene caused mutations in *Salmonella typhimurium*, whereas the monoepoxides of isoprene and parent compounds did not. In mammalian cells *in vitro*, isoprene did not cause sister chromatid exchange, chromosomal aberrations, or micronucleus formation (NTP 1995, 1999a), but did cause DNA damage in human peripheral-blood mononuclear cells and human leukemia cells when incubated with microsomal enzymes (Fabiani *et al.* 2007). In mice exposed *in vivo*, isoprene and 1,3-butadiene caused sister chromatid exchange in bone-marrow cells and micronucleus formation in peripheral-blood erythrocytes (Tice 1988, Tice *et al.* 1988). Sites at which both isoprene and butadiene caused tumors in rodents include the liver, lung, Harderian gland, forestomach, hematopoietic tissue, and circulatory system in mice and the mammary gland, kidney, and testis in rats (NTP 1999a,b). Harderian-gland tumors caused by isoprene in mice had a high frequency of unique mutations of the *K-ras* protooncogene (A to T transversions at codon 61) (Hong *et al.* 1997).

There is no evidence to suggest that mechanisms by which isoprene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to isoprene.

Properties

Isoprene is structurally similar to 1,3-butadiene and exists as a colorless, volatile liquid at room temperature (NTP 1999a). It occurs frequently in nature and is emitted to the environment by plants and trees. Isoprene is practically insoluble in water, but is soluble in ethanol, diethyl ether, benzene, and acetone. It is stable under normal conditions, but it is very flammable and will polymerize vigorously or decompose with abrupt changes in temperature or pressure (IARC 1994, Akron 2009). Physical and chemical properties of isoprene are listed in the following table.

Property	Information
Molecular weight	68.1
Specific gravity	0.681 at 20°C/4°C
Melting point	-145.95°C
Boiling point	34.07°C at 760 mm Hg
Log K_{ow}	2.42
Water solubility	0.642 g/L at 25°C
Vapor pressure	550 mm Hg at 25°C
Vapor density relative to air	2.4

Source: HSDB 2009.

Use

The majority of isoprene produced commercially is used to make synthetic rubber (*cis*-polyisoprene), most of which is used to produce vehicle tires. The second- and third-largest uses are in the production of styrene-isoprene-styrene block polymers and butyl rubber (isobutene-isoprene copolymer) (IARC 1994).

Production

Isoprene is recovered as a by-product of thermal cracking of naphtha or gas oil from C_5 streams (IARC 1994, NTP 1999a). The isoprene

yield is about 2% to 5% of the ethylene yield. U.S. demand for isoprene grew 6.5% annually from 1985 to 1992 (NTP 1999a). In 1994, isoprene production in the United States was about 619 million pounds, almost 29% more than in 1992. Estimated isoprene production capacity for eight facilities was 598 million pounds in 1996, based on estimates of isoprene content of product stream available from ethylene production via heavy liquids. In 2009, isoprene was produced by 22 manufacturers worldwide, including 12 U.S. producers (SRI 2009), and was available from 23 suppliers, including 12 U.S. suppliers (ChemSources 2009). U.S. imports of isoprene (purity \geq 95% by weight) increased from zero in 1989 to a peak of 144 million pounds in 2003. Imports declined to 19.6 million pounds in 2004, the lowest level since 1992, but remained near 32 million pounds from 2005 through 2008. During this period, U.S. exports of isoprene ranged from 7.9 million to 39.6 million pounds (in 2006) (USITC 2009). Reports filed from 1986 to 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of isoprene totaled 100 million to 500 million pounds (EPA 2004).

Exposure

Isoprene is formed endogenously in humans at a rate of 0.15 $\mu\text{mol/kg}$ of body weight per hour, equivalent to approximately 2 to 4 mg/kg per day (Taalman 1996), and is the major hydrocarbon in human breath (accounting for up to 70% of exhaled hydrocarbons) (Gelmont *et al.* 1981). Concentrations in human blood range from 1.0 to 4.8 $\mu\text{g/L}$ (Cailleux *et al.* 1992). Isoprene is produced at higher rates in males than females. The rate of isoprene production increases with age up to the age of 29 (Lechner *et al.* 2006); it is lower in young children than adults by a factor of about 2.4 (Taucher *et al.* 1997). In a study of 30 adult volunteers, the mean isoprene concentration measured in alveolar breath was 118 ppb, with a range of 0 to 474 ppb (Turner *et al.* 2006). After 20 to 30 minutes of exercise, isoprene concentration in exhaled air decreased to a range of 0 to 40 ppb (Senthilmohan *et al.* 2000). Smoking one cigarette increased the concentration of isoprene in exhaled air by 70% (Senthilmohan *et al.* 2001). Isoprene is also produced endogenously by other animals. Production rates reported for rats and mice were 1.9 and 0.4 $\mu\text{mol/kg}$ of body weight per hour, respectively (Peter *et al.* 1987).

Foods of plant origin would be expected to be a source of daily exposure to isoprene, since isoprene is emitted by agricultural crops and is the basic structural unit in countless natural products found in foods, such as terpenes and vitamins A and K (NTP 1999a). Isoprene has been reported to occur in the essential oil of oranges, the fruit of hops, carrot roots, and roasted coffee (Taalman 1996, NTP 1999a).

Isoprene is emitted from plants and trees and is present in the general environment at low concentrations (Taalman 1996). Isoprene emissions from many types of plants have been estimated under various climatic conditions, to evaluate their importance in global climate change (Mayrhofer *et al.* 2004, Parra *et al.* 2004, Schnitzler *et al.* 2004, 2005, Pegoraro *et al.* 2005, Sasaki *et al.* 2005, Sharkey 2005, Moukhtar *et al.* 2006, Simon *et al.* 2006, Tambunan *et al.* 2006). Annual global isoprene emissions, estimated at 175 billion to 503 billion kilograms (386 billion to 1,109 billion pounds), account for an estimated 57% of total global natural volatile organic compound emissions (Guenther *et al.* 1995). The average biogenic emission rate factor for isoprene in U.S. woodlands is 3 mg/m^2 per hour (compared with 5.1 mg/m^2 for total volatile organic compounds) (Guenther *et al.* 1994). Isoprene concentrations in biogenic emissions range from 8% to 91% of total volatile organic compounds, averaging 58%. Because isoprene biosynthesis is associated with photosynthesis, isoprene emissions are negligible at night (Lamb *et al.* 1993). Because isoprene is emitted

primarily by deciduous trees, emissions are seasonal, being highest in the summer and lowest in the winter (Guenther *et al.* 1994, Fuentes and Wang 1999). The south central and southeastern areas of the United States have the highest biogenic emissions (Lamb *et al.* 1993, Guenther *et al.* 1994). The half-life of atmospheric isoprene has been estimated at 0.5 hours by reaction with nitric oxide, 4 hours by reaction with hydroxyl radicals, and 19 hours by reaction with ozone (HSDB 2009).

Anthropogenic sources of isoprene in the atmosphere include ethylene production by cracking naphtha, wood pulping, oil fires, wood-burning stoves and fireplaces, other biomass combustion, tobacco smoking (200 to 400 μg per cigarette), gasoline, and exhaust from turbines and automobiles (Adam *et al.* 2006, HSDB 2009). Isoprene has been measured as one of the volatile organic compounds in the ambient air in regions with industrial pollution, and in urban, residential, and rural areas as an indicator of the potential for ozone formation. Thus, isoprene is a key indicator for regional air quality, as well as being a component of the global carbon cycle (Borbon *et al.* 2004, Guo *et al.* 2004, Kuster *et al.* 2004, Warneke *et al.* 2005, Helten *et al.* 2006).

The reported concentration of isoprene in U.S. ambient air ranges from 1 to 21 parts per billion carbon (ppbC) and generally is less than 10 ppbC. Isoprene accounts for less than 10% of non-methane hydrocarbons in ambient air. Biogenic hydrocarbons may contribute more to total atmospheric hydrocarbons under stagnant atmospheric conditions (Altschuller 1983, Hagerman *et al.* 1997). The major sources of isoprene in ambient air appear to be biogenic emissions at rural sites and vehicular emissions in urban areas (Borbon *et al.* 2001, So and Wang 2004). Where the source is primarily biogenic, the isoprene concentration slowly increases during the day, reaching a peak in the middle of the day, when photosynthesis is greatest. Where vehicular emissions are the primary source, the isoprene concentration peaks during the morning and evening rush hours and is low in the middle of the day (Borbon *et al.* 2002). One study concluded that in summer, at least 80% of the isoprene at a rural site was due to biogenic emissions, but that in winter, more than 90% of residual isoprene was from urban air-mass mixing (Borbon *et al.* 2004). Where industrial emissions are the primary source of isoprene, the concentration may peak at night, or there may be no peak at all (Zhao *et al.* 2004, Chiang *et al.* 2007).

The primary source of isoprene in indoor air is environmental tobacco smoke. Isoprene was found to be the major component of hydrocarbons in the air of a smoky café (10 patrons smoking, 10 not smoking) (16.7%) and in sidestream smoke (29.2%) (Barrefors and Petersson 1993). A monitoring survey in November 1992 in homes and workplaces in the greater Philadelphia area found mean isoprene concentrations in personal air samples of 4.65 $\mu\text{g/m}^3$ in 60 nonsmoking homes, 18.15 $\mu\text{g/m}^3$ in 29 homes with smokers, 5.29 $\mu\text{g/m}^3$ in 51 nonsmoking workplaces, and 22.80 $\mu\text{g/m}^3$ in 28 workplaces that allowed smoking (Heavner 1996). A survey in the Lower Rio Grande Valley of Texas reported a median summertime isoprene concentration of 2.90 $\mu\text{g/m}^3$ for three indoor air samples (it was not reported whether the occupants were smokers or nonsmokers), compared with 0.40 $\mu\text{g/m}^3$ for three outdoor air samples (Mukerjee 1997).

Air-monitoring data were collected at three U.S. facilities that produced isoprene monomers or polymers; 98.5% of the samples showed concentrations of less than 10 ppm, and 91.3% of less than 1 ppm (Leber 2001, Lynch 2001). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 58,000 workers in over 30 industries potentially were exposed to isoprene (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated in a more limited survey that 3,700 workers

in four industries, including 578 women, potentially were exposed to isoprene (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of isoprene on ships and barges.

Department of Transportation (DOT)

Isoprene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of isoprene is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Clean Water Act

Isoprene has been designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

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humidity at room temperature (Akron 2009). Physical and chemical properties of chlordecone are listed in the following table.

Property	Information
Molecular weight	490.6 ^a
Specific gravity	1.59 to 1.63 at 25°C ^a
Melting point	350°C (decomposes) ^a
Boiling point	434°C ^b
Log <i>K</i> _{ow}	5.41 ^a
Water solubility	2.70 mg/L 25°C ^a
Vapor pressure	2.25 × 10 ⁻⁷ mm Hg at 25°C ^a
Vapor density relative to air	16.94 ^a

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

Chlordecone was first introduced as a pesticide in 1958 and was used until 1978, when its use in the United States was discontinued (NCI 1976, IARC 1979, HSDB 2009). Chlordecone was used as an insecticide for leaf-eating insects, ants, and cockroaches, as a larvicide for flies, and for control of insects that attack structures. Chlordecone was also used on bananas, non-bearing citrus trees, tobacco, ornamental shrubs, lawns, turf, and flowers.

Production

Total U.S. production of chlordecone from 1951 to 1975 was estimated at 3.6 million pounds (ATSDR 1995). Annual production at one plant in Hopewell, Virginia, reached a peak of over one million pounds per year in 1974; production ceased in July 1975 by order of the State of Virginia (Huggett and Bender 1980). Between 90% and 99% of total chlordecone production was exported to Europe, Asia, Latin America, and Africa (ATSDR 1995). In 2009, no producers of chlordecone were identified (SRI 2009), but chlordecone was available from eight U.S. suppliers and one European supplier (ChemSources 2009).

Exposure

The primary routes of potential human exposure to chlordecone are inhalation, ingestion, and dermal contact. Chlordecone is very stable in the environment, and no degradation products have been identified. It adsorbs to particulate matter in the air, water, and soil and is removed from the atmosphere and water column by deposition and settling and from the surface soil by erosion (ATSDR 1995). When released to air, chlordecone will not directly photodegrade or react with photochemically produced hydroxyl radicals (HSDB 2009). When released to water, chlordecone adsorbs to sediment and over time is buried by sediment accumulation (Huggett and Bender 1980). Its half-life in a model river is 3.8 to 46 years (HSDB 2009). Chlordecone bioaccumulates in fish and crustaceans (Carver and Griffith 1979). When released to soil, chlordecone will adsorb to soil particles; some leaching to groundwater may occur.

In the United States, detectable levels of chlordecone were found in 400 samples of air, drinking water, plant and aquatic organisms, and municipal waste where chlordecone was manufactured (ATSDR 1995). Chlordecone has also been measured in the particulate matter and sediment in rivers on the island of Martinique in 2002 at concentrations of up to 57 µg/kg (Bocquene and Franco 2005). Bananas are the major crop in Martinique, and chlordecone was frequently used as an insecticide on banana plantations.

Concentrations of chlordecone in the environment near the Hopewell manufacturing site were 1% to 40% in dust collected one block from the plant, 1% to 2% in soil adjacent to the plant, and 2 to 6 ppm in soil at a distance of 1,000 meters from the plant (Luellen *et al.* 2006). Very high concentrations of chlordecone were detected in effluent from the Hopewell plant (0.1 to 1.0 mg/L) and in water from

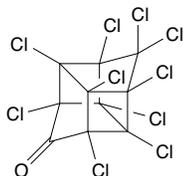
Kepone

CAS No. 143-50-0

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Kepone was formerly a registered trademark of the Allied Chemical Corporation; also known as chlordecone



Carcinogenicity

Kepone (chlordecone) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary administration of chlordecone caused liver cancer (hepatocellular carcinoma) in rats and mice of both sexes. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter in male mice exposed to chlordecone than in unexposed controls and appeared to be inversely related to exposure level in mice and rats of both sexes (NCI 1976, IARC 1979).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to chlordecone.

Properties

Chlordecone is a chlorinated polycyclic ketone that is an odorless, colorless-to-tan crystal at room temperature (HSDB 2009). It is practically insoluble in water, soluble in acetone, alcohols, ketones, and acetic acid, and less soluble in benzene and light petroleum. Chlordecone is stable to about 350°C but readily hydrates on exposure to

the plant's holding ponds (2 to 3 mg/L). However, over time, concentrations in the James River (adjacent to the plant) have fallen dramatically due to settling of chlordecone and its eventual burial in sediment (Huggett and Bender 1980). Concentrations of chlordecone in bed sediments of the James River between 1976 and 1978 ranged from undetectable ($\leq 0.01 \mu\text{g/g}$) to $5 \mu\text{g/g}$ (ATSDR 1995). Chlordecone concentrations in finfish in the James River in the 1980s reached a steady state below the action level of $0.3 \mu\text{g/g}$; however, 94% of the fish sampled since 1987 had detectable chlordecone concentrations ($\geq 0.01 \mu\text{g/g}$). Fishing restrictions remained in effect until 1989, when restrictions as a result of chlordecone contamination were removed; however, a Virginia Department of Health fish consumption advisory remained in effect as of 2006 (Luellen *et al.* 2006).

Chlordecone is also a degradation product of another insecticide, mirex (IARC 1979). Investigators have detected chlordecone in soil at a concentration of $0.02 \mu\text{g/g}$ of soil 12 years after mirex was applied at the rate of $1 \mu\text{g/g}$ of soil. Additional exposure information may be found in the Agency for Toxic Substances and Disease Registry's *Toxicological Profile for Mirex and Chlordecone* (ATSDR 1995).

At the time production ceased (in July 1975), half of the workers at the Hopewell manufacturing facility exhibited neurological symptoms. Chlordecone was measured in the blood of these exposed workers at levels of up to $11.8 \mu\text{g/mL}$. In 1976, the National Institute for Occupational Safety and Health identified 50 facilities that processed or formulated pesticides using chlordecone and estimated that about 600 U.S. workers potentially were exposed to chlordecone (NIOSH 1976).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of chlordecone = U142.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Action levels for chlordecone in fish, shellfish, and crabmeat range from 0.3 to 0.4 ppm.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.001 mg/m^3 .

Listed as a potential occupational carcinogen.

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Lead and Lead Compounds

CAS No. 7439-92-1 (Lead)

No separate CAS No. assigned for lead compounds as a class

Reasonably anticipated to be human carcinogens

First listed in the *Eleventh Report on Carcinogens* (2004)

Also known as Pb

Introduction

The compounds lead phosphate and lead acetate were first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity in experimental animals. The listing of lead and lead compounds supersedes the previous listing of lead phosphate and lead acetate in the Report on Carcinogens and applies to lead and all lead compounds.

Carcinogenicity

Lead and lead compounds are *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

Lead exposure has been associated with increased risk of lung, stomach, and urinary-bladder cancer in diverse human populations (Fu and Boffetta 1995, Steenland and Boffetta 2000, NTP 2003). The strongest epidemiological evidence is for lung and stomach cancer, which are consistently but weakly associated with occupations and industries entailing lead exposure and with indices of individual lead exposure, including job history and biological monitoring of occupationally exposed and general populations. However, most studies of lead exposure and cancer reviewed had limitations, including poor exposure assessment and failure to control for confounding by other factors that could increase the risk of cancer (such as lifestyle factors and concurrent occupational exposure to other carcinogens), and did not demonstrate relationships between the level or duration of exposure and the magnitude of cancer risk. The crude exposure measures used in most studies, such as treating whole plants or occupations as having uniform exposure, may have limited the magnitude of risk estimates, most of which were modest. Evidence from epidemiological studies therefore is compatible with small increases in the risk of lung or stomach cancer; however, this evidence must be weighed against the potential for confounding by factors such as smoking, diet, or coexposure to arsenic.

Cancer Studies in Experimental Animals

Lead compounds caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Carcinogenicity was observed in studies with inorganic lead compounds, both soluble (lead acetate and lead subacetate) and insoluble (lead phosphate, lead chromate), and with tetraethyl lead (an organic lead compound). Lead caused cancer in rats and/or mice exposed orally, by injection, or perinatally (via the pla-

centa or lactation). Benign and malignant kidney tumors (adenoma, carcinoma, and adenocarcinoma) were most frequently associated with lead exposure, and tumors of the brain, hematopoietic system, and lung were reported in some studies (IARC 1980, 1987).

Lead subacetate administered in the diet caused benign and malignant kidney tumors (adenoma and carcinoma or adenocarcinoma) in mice and rats of both sexes and brain tumors (glioma) in rats, and its administration by intraperitoneal injection caused benign lung tumors (adenoma) in mice. Lead acetate administered in the diet or drinking water caused benign and malignant kidney tumors (adenoma and carcinoma) in rats and increased the incidence of virus-induced lymphocytic leukemia in mice. After pregnant mice were given lead acetate in the drinking water from gestation day 12 to four weeks postpartum, the offspring showed a dose-related increase in proliferative lesions of the kidneys (including atypical hyperplasia, adenoma, and adenocarcinoma) (Waalkes *et al.* 1995). Rats exposed to lead phosphate by subcutaneous injection (alone or followed by intraperitoneal injection) developed benign or malignant kidney tumors (adenoma or carcinoma). Rats exposed to lead chromates by subcutaneous injection developed cancer at the injection site (sarcoma), and administration of lead chromates by intramuscular injection caused kidney cancer (renal-cell carcinoma) (IARC 1990). (Because lead chromate is also a hexavalent chromium compound, it is also included in the listing for Chromium Hexavalent Compounds.) Tetraethyl lead administered by subcutaneous injection caused lymphoma in female mice. Exposure to lead naphthenate, lead carbonate, lead arsenate, lead nitrate, and metallic lead (as lead powder) did not significantly increase tumor incidences in experimental animals (IARC 1980).

Studies on Mechanisms of Carcinogenesis

Exposure of rodents to lead compounds also increased the incidence or accelerated the appearance of kidney tumors induced by other carcinogens, including *N*-ethyl-*N*-hydroxyethylnitrosamine and *N*-(4'-fluoro-4-biphenyl)acetamide. Higher incidences of kidney and liver cancer were observed in rats fed diets containing lead subacetate and 2-acetylaminofluorene than in rats fed either lead subacetate or 2-acetylaminofluorene alone (IARC 1980, 1987).

Absorption of lead is affected by age, the chemical form of the lead, and minerals in the diet (e.g., iron, calcium, and zinc) (ATSDR 1999). Gastrointestinal absorption of lead is greater in children than in adults (Hammad *et al.* 1996). Once absorbed, lead is distributed to blood plasma, the nervous system, and soft tissues. It subsequently is redistributed and accumulates in bone; 75% to 90% of the lead body burden is found in bones and teeth.

In studies of humans occupationally exposed to lead, there is evidence to suggest that lead damages chromosomes or DNA. In most studies, lead caused micronucleus formation, chromosomal aberrations, and DNA damage, but studies on sister chromatid exchange gave conflicting results. Genetic studies on humans environmentally exposed to lead also gave conflicting results. Lead did not cause mutations in bacteria, and results from test systems using mammalian cells were conflicting. Lead caused chromosomal aberrations in most studies in plants or mammals, both *in vitro* and *in vivo*. It caused DNA damage or fragmentation in mammals *in vivo* and in cell-free systems (in the presence of hydrogen peroxide), but mammalian *in vitro* studies gave conflicting results. Lead also inhibited the activity of DNA and RNA polymerase in cell-free systems and in mammalian cell cultures. Conflicting results were observed for sister chromatid exchange and micronucleus formation in mammalian test systems (*in vitro* and *in vivo*) (ATSDR 1999, NTP 2003).

The mechanisms by which lead causes cancer are not understood. Lead compounds do not appear to cause genetic damage directly, but may do so through several indirect mechanisms, including inhibition of DNA synthesis and repair, oxidative damage, and interaction with DNA-binding proteins and tumor-suppressor proteins (NTP 2003).

Properties

Elemental lead is an odorless, silver-bluish-white metal that is insoluble in water (Budavari *et al.* 1996, Lide and Frederikse 1998, HSDB 2009). It is soft, highly malleable, ductile, and a relatively poor conductor of electricity. It is resistant to corrosion but tarnishes upon exposure to air. Lead exists in the valence states of +2 and +4 and has four naturally occurring stable isotopes: ²⁰⁴Pb, ²⁰⁶Pb, ²⁰⁷Pb, and ²⁰⁸Pb. Inorganic lead compounds usually consist of lead in the divalent state (+2), and the chemistry of divalent lead is similar to that of group 2 metals (beryllium, magnesium, calcium, strontium, and barium).

Lead compounds may be divided between those compounds that are relatively soluble in water and those that are relatively insoluble in water. Compounds are considered soluble or insoluble based on the following criteria: (1) If a solubility constant (K_{sp}) is available, a compound with a value greater than or equal to the K_{sp} for lead chloride (1×10^{-4}) is considered soluble. (2) If a K_{sp} is not available, a compound is considered soluble if more than 2 g of the compound dissolves in 100 mL of water. (3) If no numeric solubility data are available, the compounds are considered soluble or insoluble according to the general rules of solubility.

The major soluble lead compounds are lead acetate, lead acetate trihydrate, lead chloride, lead nitrate, and lead subacetate; all are soluble in water, and lead acetate trihydrate is miscible with water. Lead acetate exists as colorless or white crystals, granules, or powders that are soluble in glycerol and slightly soluble in ethanol. Lead acetate trihydrate occurs as white crystals that are slightly soluble in ethanol and acetone. Lead chloride exists as a white crystalline powder that is insoluble in ethanol. Lead nitrate occurs as colorless or white crystals that are insoluble in nitric acid. Lead subacetate is a white heavy powder that is soluble in ethanol (HSDB 2009).

The major insoluble lead compounds include 17 inorganic lead compounds. Lead arsenate, lead azide, lead bromide, lead fluoride, lead phosphate, lead stearate, lead sulfate, and lead thiocyanate occur as white powders, crystals, or needles. Lead carbonate occurs as colorless rhombic crystals, and lead fluoborate occurs as a colorless crystalline powder. Lead chromate, lead iodide, lead naphthenate, lead oxide, and lead styphnate occur as yellow to reddish-yellow powder, crystals, or paste. Lead sulfide occurs as metallic black cubic crystals, and lead tetraoxide is a bright-red heavy powder. Lead arsenate, lead fluoride, and lead phosphate are soluble in nitric acid, and lead arsenate, lead carbonate, lead oxide, lead phosphate, lead sulfate, and lead thiocyanate are soluble in potassium hydroxide or other alkalis. Lead bromide, lead iodide, lead oxide, lead phosphate, and lead sulfate are insoluble in alcohol, and lead fluoborate decomposes in alcohol. Lead tetraoxide is soluble in hydrochloric and acetic acids and insoluble in ethanol. The reported melting points of these compounds range from 100°C (lead naphthenate) to 1,170°C (lead sulfate). All of the insoluble inorganic lead compounds have high boiling points (up to 1,470°C); however, lead carbonate decomposes before it boils, and lead azide explodes at 350°C. Most of these compounds have high specific gravities, ranging from 6.2 for lead sulfate to 9.53 for lead oxide, but a few have lower specific gravities, including lead naphthenate (1.15), lead fluoborate (1.75), and lead thiocyanate (3.82) (HSDB 2009, Akron 2010).

Tetraethyl lead and tetramethyl lead are insoluble organic lead compounds. They both exist as colorless liquids and are soluble in

benzene, ethanol, and diethyl ether. The octanol-water partition coefficients are 4.15 for tetraethyl lead and 2.97 for tetramethyl lead (HSDB 2009). The following table lists physical and chemical properties for lead, the major soluble inorganic lead compounds, and the organic lead compounds.

Substance	Specific gravity	Melting pt.	Boiling pt.
Lead	11.34	327°C	1,740°C
Lead acetate	3.25	280°C	dec
Lead acetate trihydrate	2.55	75°C	200°C (dec)
Lead chloride	5.85	501°C	950°C
Lead nitrate	4.53	470°C	dec
Lead subacetate	NR	75°C	dec
Tetraethyl lead	1.659	-136.8°C	200°C
Tetramethyl lead	1.995	-30.2°C	110°C

Source: HSDB 2009. dec = decomposes. NR = not reported.

Use

In worldwide metal use, lead ranks behind only iron, copper, aluminum, and zinc (Howe 1981). Its largest use is in lead-acid storage batteries for motor vehicles and general industry. Lead metal also is commonly used for ammunition, cable covering, piping, brass and bronze, bearing metals for machinery, and sheet lead (ATSDR 1999).

All of the major soluble lead compounds have industrial uses. Lead acetate is used as a water repellent, for mildew protection, and as a mordant for cotton dyes. Lead acetate trihydrate is used in varnishes, chrome pigments, and as an analytical reagent, and lead chloride is used in asbestos clutch or brake linings, as a catalyst, and as a flame retardant. Lead nitrate is used in the manufacture of matches and explosives, as a heat stabilizer in nylon, and as a coating on paper for photothermography. Lead subacetate is used in sugar analysis and for clarifying solutions of organic substances (HSDB 2009).

The insoluble lead compounds also have a variety of uses. Lead azide and lead styphnate both are used in munitions manufacture. Lead carbonate, lead fluoride, lead fluoborate, and lead naphthenate are used as catalysts, with additional uses in the electronic and optical industries (lead fluoride), in coatings for thermographic copying (lead carbonate), as a curing agent for epoxy resins (lead fluoborate), and as a varnish drier (lead naphthenate). Lead phosphate and lead stearate both are used as stabilizers in the plastics industry. Lead iodide and lead sulfate are used in photography; lead iodide is also used in thermoelectric materials, and lead sulfate with zinc in galvanic batteries. Lead oxide and lead sulfide are used in ceramics; lead oxide is also used as a vulcanizing agent in rubber and plastics, and lead sulfide as a humidity sensor in rockets. Lead chromate is used as a pigment in paints, rubber, and plastics; lead tetraoxide is used in plasters, ointments, glazes, and varnishes; and lead thiocyanate is used in the manufacture of safety matches and cartridges. Lead arsenate formerly was used as an insecticide and herbicide, but no current uses were found.

Organic lead (including tetraethyl lead and tetramethyl lead) was widely used in the United States as an anti-knock additive in motor-vehicle fuels until the U.S. Environmental Protection Agency initiated a phase-out of leaded gasoline in the early 1970s. By 1988, the total lead used in gasoline had been reduced to 1% of the 1970 level; in 1996, the use of lead in fuel for on-road motor vehicles was totally banned. Despite the legislated end to use of lead as a gasoline additive and reductions in some other uses of lead, overall U.S. lead consumption continued to grow until 1999, mainly because of increased production of lead-acid batteries (ATSDR 1999), but has since been on a general decline (USGS 2009, 2010, Guberman 2010).

Production

Lead is refined from mined ore, which occurs most frequently in the form of lead sulfide, also known as galena (Howe 1981). Mined lead ore is crushed and ground, and a lead concentrate is formed by separation of the various minerals. The lead concentrate is shipped to a primary smelter for refining. At the smelter, lead concentrates are sintered, roasted, and refined into lead metal that is 99.99% pure. However, secondary lead, produced from recycled scrap (primarily from lead acid batteries), accounts for the majority of lead produced in the United States.

In 2009, 400,000 metric tons (882 million pounds) of lead was mined in the United States, a slight decline from levels over the previous four years (USGS 2010). Primary lead production in the United States has declined steadily over the past several decades, from a high of 626,000 metric tons (1.4 billion pounds) in 1970 to 115,000 metric tons (254 million pounds) in 2009 (USGS 2009, 2010). In contrast, secondary lead production has increased steadily over the same period, from 450,000 metric tons (992 million pounds) in 1970 to 1,120,000 metric tons (2.5 billion pounds) in 2009, when it accounted for about 90% of the total refined lead produced in the United States. In 2009, five lead mines in Missouri, plus lead-producing mines in Alaska and Idaho, yielded most of the mined lead in the United States. Lead was processed at one smelter-refinery in Missouri. Of the 21 plants that produced secondary lead, 15 accounted for over 99% of secondary production (USGS 2010).

From 1980 to 1999, lead consumption in the United States rose steadily from 906,000 metric tons (2 billion pounds) to 1,760,000 metric tons (3.9 billion pounds), but consumption has since generally declined; in 2009, it was 1,420,000 metric tons (3.1 billion pounds). In 2009, lead was consumed at 76 manufacturing plants, with lead-acid battery production accounting for 88% of U.S. lead consumption. U.S. imports and exports of lead have fluctuated widely over the past several decades. Imports have ranged from a low of 85,000 metric tons (187 million pounds) in 1980 to a high of 365,000 metric tons (805 million pounds) in 2000; imports in 2009 were 275,000 metric tons (606 million pounds). Exports of refined lead metal have ranged from a low of 5,000 metric tons (11 million pounds) in 1976 to a high of 164,000 metric tons (362 million pounds) in 1980; exports in 2009 were 85,000 metric tons (187 million pounds) (USGS 2010).

Lead acetate was first produced in the United States in 1944; however, little production information was found. Three companies reported production of an undisclosed amount of lead acetate in 1977. Production volumes were estimated at over 6,810 kg (15,000 lb) in 1978 and over 2,270 kg (5,000 lb) in 1982, and U.S. imports were 113 kg (250 lb) in 1978 and 39,300 kg (87,000 lb) in 1982 (IARC 1980, HSDB 2009). Lead nitrate was first commercially produced in the United States in 1943, and imports of 480,000 kg (1.06 million pounds) were reported in 1978. Commercial production of lead subacetate was first reported in the United States in 1947; no production data were found (IARC 1980).

Lead carbonate has been produced commercially in the United States since the 1600s; in 1976, U.S. production was 1.48 million kilograms (3.3 million pounds), with imports in 1978 of 178,000 kg (392,000 lb) (IARC 1980). U.S. exports of lead carbonate in 2002 were 779,071 kg (1.7 million pounds) (USITC 2003). U.S. production of lead oxide in 1976 was 120 million kilograms (260 million pounds), with imports of 20 million kilograms (44 million pounds) (IARC 1980). U.S. imports of lead oxides in 2002 totaled 3.9 million kilograms (8.6 million pounds), and exports totaled 1.7 million kilograms (3.7 million pounds) (USITC 2003). Commercial production of lead naphthenate in the United States was first reported in 1944. Production of lead naphthenate was 8.2 million kilograms (18.1 million pounds)

in 1969, dropping to 2.2 million kilograms (4.9 million pounds) in 1977. U.S. production of lead tetraoxide in 1976 was 18 million kilograms (39.7 million pounds), with imports of 800,000 kg (1.8 million pounds) in 1976 and 1 million kilograms (2.2 million pounds) in 1979, and exports were estimated at 1 million to 15 million kilograms (2.2 million to 33 million pounds) in 1977 (IARC 1980).

Tetraethyl lead was first produced commercially in the United States in 1923. Production was 266 million kilograms (590 million pounds) in 1964, dropping to 148 million kilograms (330 million pounds) in 1977. U.S. imports of tetraethyl lead in 1978 were 17,000 kg (37,500 lb). Commercial production of tetramethyl lead in the United States began in 1960; 54 million kilograms (119 million pounds) was produced in 1977, and 13,800 kg (30,400 lb) was imported in 1974 (IARC 1980).

Exposure

The routes of environmental exposure to lead resulting in its absorption into the body are inhalation (with 30% to 50% of the inhaled dose absorbed into the bloodstream), ingestion (with 8% to 15% of the ingested dose absorbed into the bloodstream) and, to a limited extent, dermal contact. Lead is released to the environment from both natural and anthropogenic sources; however, most exposure results from anthropogenic sources (e.g., mining, smelting, industrial uses). Lead exists in various inorganic and organic forms, which affect its environmental fate, transport, and bioavailability. Regardless of the form, however, lead is not degraded and remains available for exposure. In the mid 1980s, combustion of leaded gasoline contributed about 90% of all anthropogenic lead emissions, but the percentage decreased sharply through the late 1990s as a result of the phase-out of leaded gasoline (ATSDR 1999, EPA 2003). Over 90% of the lead released from the combustion of leaded gasoline was in the form of inorganic lead halides (e.g., lead bromochloride), while less than 10% was in the form of organic lead alkyls (e.g., tetraethyl lead). Tetraalkyl lead compounds once accounted for 5% to 10% of the total particulate lead present in the atmosphere but are no longer present in significant quantities. Industrial processes, particularly lead smelters, are now the primary source of lead emissions and accounted for more than 78% of emissions in 2001 (EPA 2003).

According to EPA's Toxics Release Inventory, over 4,000 facilities released almost 22 million pounds of lead and 482 million pounds of lead compounds to the environment in 2007 (TRI 2009). Concentrations of lead in the air in the United States declined by 97% between 1976 and 1995 and by 57% between 1993 and 2002 (ATSDR 1999, EPA 2003). Ambient concentrations are highly variable but may exceed 10 $\mu\text{g}/\text{m}^3$ near industrial sources such as smelters (ATSDR 1999). A 1991 survey of lead levels in U.S. urban air found a maximum quarterly mean concentration of approximately 0.08 $\mu\text{g}/\text{m}^3$. Lead concentrations typically are lower in rural areas. In 1995, the estimated U.S. mean air lead concentration was 0.04 $\mu\text{g}/\text{m}^3$ (EPA 1996). The estimated daily average intake of lead by inhalation in 1991 was 2 μg for an adult living in a U.S. urban setting, significantly lower than estimates from the early 1980s (ATSDR 1999).

Lead concentrations in U.S. drinking water generally are below 5 $\mu\text{g}/\text{L}$. Lead also is found in food, cigarette smoke, and alcoholic beverages. Levels in food have declined since the elimination of lead-soldered food cans between 1979 and 1989 (ATSDR 1999). In 1990, the estimated daily intake of lead from consumption of food, water, and beverages was approximately 4 μg for children aged 2 years or younger, 6 to 9 μg for children aged 14 to 16, 6 to 9 μg for adults aged 25 to 30, and 2 to 8 μg for adults aged 60 to 65. For young children, the most common source of environmental lead exposure is direct ingestion of paint chips and lead-laden dust and soil released from

aging painted surfaces. These sources can contribute an additional daily intake of 5 μg for a toddler engaging in normal hand-to-mouth activity (CDC 1997, Lanphear *et al.* 1998).

The most common route of occupational exposure to lead is inhalation of lead fumes or lead-laden dusts in air and absorption of lead through the respiratory system. Lead may also be ingested and absorbed via the gastrointestinal tract (Bress and Bidanset 1991, Stauber *et al.* 1994). The National Institute for Occupational Safety and Health has estimated that more than three million Americans potentially are occupationally exposed to some form of lead (Staudinger and Roth 1998). Occupations having frequent high exposure to lead include battery-production worker, battery-recycling worker, foundry worker, lead chemical worker, lead smelter and refinery worker, leaded-glass worker, pigment worker, and radiator-repair worker. Occupations with a moderate frequency of high exposure include firing-range instructor, house renovator, lead miner, newspaper printer, plastics worker, rubber worker, and steel welder or cutter. Occupations with a low frequency of high exposure include automobile-repair worker, cable-production worker, construction worker, demolition worker, firing-range participant, flame-solder worker, plumber or pipe fitter, pottery-glaze producer, ship-repair worker, and stained-glass producer (Fu and Boffetta 1995, ATSDR 1999). For U.S. industries identified by the Occupational Safety and Health Administration as having significant airborne lead in the workplace, the mean concentration ranged from 165 $\mu\text{g}/\text{m}^3$ at secondary smelters to 200 $\mu\text{g}/\text{m}^3$ at storage-battery plants and brass, bronze, and copper foundries (Froines *et al.* 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Accessible parts of products designed or intended primarily for children 12 and younger may not contain more than 300 ppm of lead; products exceeding this level are banned hazardous substances.

Paint or any other surface-coating materials for consumer use shall not contain lead at levels greater than 90 ppm.

Toys and other items for child use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film are banned.

Furniture articles for consumer use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film are banned.

Metal-cored candlewicks containing more than 0.06% lead by weight in the metal, and candles with such wicks, are banned.

Department of Transportation (DOT)

Numerous specific lead compounds, and lead compounds not otherwise specified, are considered hazardous materials and marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Ambient Air Quality Standards: National primary and secondary ambient air quality standard = 1.5 $\mu\text{g}/\text{m}^3$ for lead and lead compounds.

National Emissions Standards for Hazardous Air Pollutants: Lead compounds are listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of tetraethyl lead and tetramethyl lead is subject to provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb for tetramethyl lead.

Urban Air Toxics Strategy: Lead compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Mobile Source Air Toxics: Lead compounds are listed as a mobile source air toxic for which regulations are to be developed.

As defined by the Clean Air Act, gasoline which contains lead additives or contains lead at a concentration greater than 0.05 g/gal shall not be sold for use in motor vehicles.

Clean Water Act

Biosolids Rule: Limits have been established for lead in biosolids (sewage sludge) when used or disposed of via land application or incineration.

Effluent Guidelines: Lead and lead compounds are listed as toxic pollutants.

Numerous lead compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb for lead, lead acetate, lead chloride, lead fluoroborate, lead fluoride, lead iodide, lead nitrate, lead phosphate, lead stearate, lead subacetate, lead sulfate, lead sulfide, lead thiocyanate, and tetraethyl lead; = 1 lb for lead arsenate.

Emergency Planning and Community Right-To-Know Act

Toxic Release Inventory: Lead and lead compounds are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 10 lb for tetraethyl lead; = 100 lb for tetramethyl lead.
Threshold planning quantity (TPQ) = 100 lb for tetraethyl lead and tetramethyl lead.

Federal Insecticide, Fungicide, and Rodenticide Act

All registrations for pesticides that have lead arsenate as an active ingredient have been canceled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 5.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of lead or lead compounds = F035, F037, F038, K002, K003, K005, K046, K048, K049, K051, K052, K061, K062, K064, K069, K086, K100, K176, P110, P116, U144, U145, U146.

Lead and lead compounds are listed as hazardous constituents of waste.

Safe Drinking Water Act

Treatment technique, action level = 0.015 mg/L for lead.

Numerous requirements have been established to reduce exposure to lead in drinking water due to lead leaching from lead pipes and lead fittings.

Toxic Substances Control Act

A seller must disclose to the purchaser of a home any known lead-based paint hazards.

Comprehensive regulations have been developed to prevent lead-based paint poisoning in certain residential structures.

Food and Drug Administration (FDA)

A conspicuous label shall be on the surface of ornamental or decorative ceramics that contain lead warning that the vessel is not for food use and may be harmful if used for such.

A number of food additives generally recognized as safe are permitted for use in foods for human consumption providing maximum lead levels do not exceed concentrations prescribed in 21 CFR 84.

Action levels for lead in ceramic ware, hollowware, cups, mugs, and pitchers range from 0.5 to 7 µg/mL of leaching solution.

Lead acetate hair coloring must provide warning labels and may be safely used in cosmetics intended for coloring hair on the scalp if lead levels do not exceed 0.6% (weight to volume).

Lead solder may not be used in food packaging.

Maximum allowed levels of lead in various color additives used in food, drugs, cosmetics, and medical devices are provided 21 CFR 73 and 74.

Maximum permissible level of lead in bottled water = 0.005 mg/L.

Select food additives are permitted for use in animal feed with maximum lead levels ranging from 10 to 30 ppm.

Restrictions on the use of lead in various food additives are prescribed in 21 CFR 172.

Limits on the use of lead in feed and drinking water of animals are prescribed in 21 CFR 584.

Tin-coated lead foil capsules shall not be used for wine bottles.

Department of Housing and Urban Development (HUD)

HUD's Lead-Based Paint Disclosure Rule requires that a seller or lessor disclose to the purchaser the presence of any lead-based paint in a home for sale, provide an EPA pamphlet on the health effects of lead, provide records on lead-based paint used in home, and provide a 10-day period to conduct a home inspection for lead-based paint or lead-based paint hazards.

HUD has established regulations to implement the provisions set forth in the Residential Lead-Based Paint Hazard Reduction Act. In part, the goals of these regulations are to develop a national strategy to build the infrastructure necessary to eliminate lead-based paint hazards in all housing as expeditiously as possible, and to ensure that the existence of lead-based paint hazards is taken into account in the development of government housing policies and in the sale, rental, and renovation of homes and apartments.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.050 mg/m³ for metallic lead, inorganic lead compounds, and organic lead soaps.

Comprehensive standards have been developed for occupational exposure to metallic lead, all inorganic lead compounds, and organic lead soaps.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.05 mg/m³ for lead, inorganic lead compounds, and lead chromate; = 0.15 mg/m³ for tetramethyl lead; = 0.1 mg/m³ for tetraethyl lead.

Consumer Product Safety Commission (CPSC)

Manufacturers are requested to eliminate the use of lead that may be accessible to children from products used in or around households, schools, or in recreation.

It is recommended that before purchasing products for resale, importers, distributors, and retailers make assurances that those products do not contain lead that may be accessible to children.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.05 mg/m³ (as metallic lead) for metallic lead, lead oxides, and lead salts (including organic salts such as lead soaps but excluding lead arsenate); = 0.002 mg/m³ (as arsenic) for lead arsenate (15-min exposure) (listing for inorganic arsenic compounds).

Immediately dangerous to life and health (IDLH) limit = 100 mg/m³ (as metallic lead).

Air concentrations should be maintained so that worker blood-lead levels remain at less than 0.06 mg Pb/100 g of whole blood.

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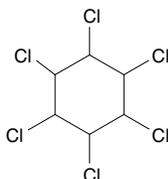
Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers

CAS No. 58-89-9 (Lindane)

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Lindane is also known as γ -hexachlorocyclohexane



Carcinogenicity

Lindane (as γ -hexachlorocyclohexane), hexachlorocyclohexane (technical grade), and other hexachlorocyclohexane isomers are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to technical-grade hexachlorocyclohexane or individual isomers caused tumors in rodents at two different tissue sites. Dietary administration of technical-grade hexachlorocyclohexane (66.5% α isomer, 11.4% β isomer, 15.2% lindane, 6.4% δ isomer, and 0.5% other isomers), lindane, α - or β -hexachlorocyclohexane, or mixtures of various isomers caused liver tumors in both sexes of several strains of mice (IARC 1979). Dietary administration of the α isomer also caused liver tumors in rats (Schulte-Hermann *et al.* 1981, IARC 1987). In addition, dietary exposure to technical-grade hexachlorocyclohexane caused tumors of the lymphoreticular system in mice of both sexes (Kashyap *et al.* 1979, IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to hexachlorocyclohexane or its isomers. Three cases of leukemia (paramyeloblastic and myelomonocytic) were reported in men exposed to lindane with or without coexposure to other chemicals (IARC 1974, 1979). Many cases of aplastic anemia have also been associated with exposure to hexachlorocyclohexane or lindane, and death from lung cancer was increased among agricultural workers who had used hexachlorocyclohexane (unspecified) and a variety of other pesticides and herbicides.

Properties

Hexachlorocyclohexane isomers, including lindane, are organochlorine pesticide compounds that are brownish to white crystalline powders with a penetrating musty odor (IARC 1974). Technical-grade hexachlorocyclohexane is a mixture of several hexachlorocyclohexane isomers. Each isomer has slightly different physical and chemical properties, including solubilities. The α isomer is practically insoluble in water but soluble in chloroform and benzene. The β isomer is very slightly soluble in water and slightly soluble in chloroform and benzene. The γ isomer (lindane) is practically insoluble in water but

very soluble in chloroform, ethanol, acetone, ether, and benzene. The δ isomer is practically insoluble in water but soluble in ethanol, ether, and benzene. Technical-grade lindane (99% γ isomer) (HSDB 2009) is stable under normal temperature and pressure (Akron 2009). Physical and chemical properties of α -, β -, γ -, and δ -hexachlorocyclohexane (HCH) are listed in the following table.

Property	α -HCH	β -HCH	γ -HCH	δ -HCH
Molecular weight	290.8	290.8	290.8	290.8
Specific gravity	1.87	1.89	1.85	NA
Melting point	158°C	309°C	112.5°C	141.5°C
Boiling point	288°C	60°C at 0.50 mm Hg	323.4°C at 760 mm Hg	60°C at 0.36 mm Hg
Log K_{ow}	3.8	3.78	3.72	4.14
Water solubility	0.002 g/L ^a	0.0002 g/L ^b	0.0073 g/L ^a	0.0314 g/L ^a
Vapor pressure	4.5×10^{-5} mm Hg ^a	3.6×10^{-7} mm Hg ^b	4.20×10^{-5} mm Hg ^b	3.5×10^{-5} mm Hg ^a

Source: HSDB 2009. NA = not available. ^aAt 25°C. ^bAt 20°C

Use

The only identified uses for hexachlorocyclohexane-containing products are based on the insecticidal activity of the γ isomer (lindane), which is considered to be the only insecticidally effective component (Exttoxnet 1996). Lindane or technical-grade hexachlorocyclohexane containing the γ isomer is used primarily as an insecticide in the treatment of wood and wooden structures, seed grains, and livestock (ATSDR 2005, HSDB 2009). Other major uses are as an insecticide for several dozen fruit and vegetable crops, in baits and seed treatments for rodent control, and for treatment of scabies (mites) and lice. It is approved by the U.S. Food and Drug Administration for use in three products for the treatment of lice and scabies (one lotion and two shampoos) (FDA 2009). Agricultural and pesticide uses accounted for about 270,000 kg (594,000 lb) of lindane and 450,000 kg (1 million pounds) of technical-grade hexachlorocyclohexane in 1974; the remaining uses were industrial or pharmaceutical (IARC 1979).

Production

Technical-grade hexachlorocyclohexane is produced as a mixture of isomers (primarily the α , β , γ , δ , and ϵ isomers) by photochlorination of benzene, a reaction that can be started by free-radical initiators such as visible or ultraviolet light, X-rays, or gamma rays (ATSDR 2005). The active γ -hexachlorocyclohexane (lindane) can be concentrated by treatment with methanol or acetic acid, followed by fractional crystallization, which produces technical grade lindane containing 99.9% γ isomer. Commercial production of lindane in the United States began in 1945 and peaked in the 1950s, when 17.6 million pounds was manufactured (IARC 1974). Lindane is no longer produced commercially in the United States, but it is produced by 13 manufacturers worldwide, including 7 in India and 4 in China (SRI 2009), and is available from 42 suppliers, including 19 U.S. suppliers (ChemSources 2009). U.S. imports of hexachlorocyclohexane increased from 310,000 lb to 1.4 million pounds between 1989 and 1999 imports, declining to zero in 2005 and remaining zero through 2008 except in 2006, when 73,000 lb was imported. U.S. exports of hexachlorocyclohexane increased from zero in 1990 to 1.5 million pounds in 2005, declining to 154,000 lb in 2008 (USITC 2009).

Exposure

The routes of potential human exposure to lindane and other hexachlorocyclohexane isomers are ingestion, inhalation, and dermal contact (HSDB 2009). The general population potentially is exposed through consumption of foodstuffs contaminated with pesticide residues. According to U.S. Food and Drug Administration's Total Diet

Survey, lindane was detected in 279 of 2,168 samples and in at least one sample of all 54 different food items analyzed (FDA 2006). Most of the food items in which lindane was detected had significant fat content; however, the highest lindane concentrations were in pickles and raw mushrooms, which have low fat content. Daily dietary intake of hexachlorocyclohexane isomers by the adult U.S. population was estimated at 0.010 µg/kg (10 ng/kg) of body weight for all isomers and 0.002 µg/kg (2 ng/kg) for lindane. For 1982 to 1984, the estimated dietary intake of lindane was 1.9 ng/kg of body weight for infants aged 6 to 11 months and 7.9 ng/kg for toddlers aged two years, who had the highest average daily intake. By 1986 to 1991, daily intake had fallen to 0.8 ng/kg for infants and 3.2 ng/kg for toddlers (ATSDR 2005).

Dermal exposure occurs when shampoos and lotions containing lindane are used for the treatment of lice and scabies (FDA 2009). The highest average blood concentration of lindane measured in children after scabies treatment with one of these products was 0.028 µg/mL (ATSDR 2005).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of lindane ranged from 314 and 2,118 lb between 1988 and 1997. In 1998, over 25,000 lb was sent to a hazardous-waste landfill. By 2006, releases had declined to 10 lb. In 2007, five facilities released a total of 1,555 lb of lindane, mostly off site for unspecified management (TRI 2009). Lindane was found in at least 189 hazardous-waste sites currently or formerly on the National Priorities List; it occurred in air at 9 sites, surface water at 33 sites, sediment at 36 sites, and soil at 90 sites. The Non-Occupational Pesticide Exposure Study, published in 1990, collected personal air samples at one U.S. location with high pesticide usage and one with low to medium usage. The range of mean γ -hexachlorocyclohexane concentration was 7 to 22 ng/m³ at the high-usage site and 0.7 to 5 ng/m³ at the low- to medium-usage site (ATSDR 2005).

Hexachlorocyclohexane isomers have been detected in human fatty tissue, blood, and breast milk. The National Human Adipose Tissue Survey (NHATS), conducted in 1982, found β -hexachlorocyclohexane in 87% of composite post-mortem samples of fatty tissue. According to NHATS data, the mean concentration of β -hexachlorocyclohexane in fat decreased from 0.45 ppm in 1970 to 0.16 ppm in 1981. The levels were highest in the southern United States. In the 1970s, the National Health and Nutrition Examination Survey (NHANES) found β -hexachlorocyclohexane in blood at a median concentration of 1.7 ppb. When the NHANES was repeated in 1999 to 2000, the geometric mean concentration of β -hexachlorocyclohexane and γ -hexachlorocyclohexane in serum lipid was 9.68 ng/g (ppb) for individuals over 12 years of age (ATSDR 2005). β -Hexachlorocyclohexane was measured in breast milk at a concentration of 0.6 ng/g in Canadian populations living near the Great Lakes. In the Netherlands, concentrations of γ -hexachlorocyclohexane in breast-milk fat in 1988 ranged from 0.01 to 0.24 mg/kg (HSDB 2009). Many other studies in populations throughout the world, especially Arctic populations, have found hexachlorocyclohexane isomers in blood, fat, and breast-milk samples. Hexachlorocyclohexane isomers have been measured at higher concentrations in all types of samples in areas of the world where lindane is still extensively used for pest control, such as India and Africa.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 15,036 workers, including 5,153 women, potentially were exposed to lindane (NIOSH 1990). No occupational exposure data were found for other hexachlorocyclohexane isomers.

Regulations

Department of Transportation (DOT)

Lindane is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Lindane (all isomers) is listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Hexachlorocyclohexane is listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.98 µg/L for lindane; = 0.0026 µg/L for the α isomer; = 0.0091 µg/L for the β isomer; based on fish or shellfish consumption only = 1.8 µg/L for lindane; = 0.0049 µg/L for the α isomer; = 0.017 µg/L for the β isomer.

Lindane is designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb for lindane, all isomers.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Lindane and α -hexachlorocyclohexane are listed substances subject to reporting requirements.

Reportable quantity (RQ) = 1 lb for lindane.

Threshold planning quantity (TPQ) = 1,000 lb for lindane solid in powder form with particle size < 100 µm or solution or molten form; = 10,000 lb for lindane in all other forms.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerances for lindane residue in various animal fats range from 4 to 7 ppm.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.4 mg/L for lindane.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of lindane or hexachlorocyclohexane = U129, F024.

Lindane is listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0002 mg/L for lindane.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0002 mg/L for lindane.

Action levels for lindane in food and in animal feed range from 0.1 to 0.5 ppm.

Lindane is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.5 mg/m³ for lindane.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m³ for lindane.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.5 mg/m³ for lindane.

Immediately dangerous to life and health (IDLH) limit = 50 mg/m³ for lindane.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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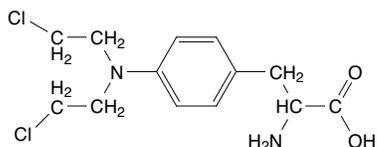
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Melphalan

CAS No. 148-82-3

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Melphalan is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies found that patients treated with melphalan for breast cancer, ovarian cancer, and bone-marrow cancer (multiple myeloma) had an increased risk of leukemia (relative risk > 100). The risk of leukemia increased with increasing dose of melphalan but was not affected by co-exposure to radiation therapy (IARC 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of melphalan from studies in experimental animals. When administered by intraperitoneal injection, melphalan caused cancer of lymphatic tissue (lymphosarcoma) in male mice, lung tumors in mice of both sexes, and cancer of the abdominal cavity (sarcoma of the peritoneum) in rats of both sexes (IARC 1975, 1987).

Properties

Melphalan is an alkylating agent that is a white to buff odorless powder at room temperature. It is practically insoluble in water, insoluble

in chloroform and ether, slightly soluble in methanol, and soluble in ethanol, propylene glycol, 2% carboxymethylcellulose, and alkaline and dilute acid solutions. It hydrolyzes in aqueous solution (IARC 1975). Physical and chemical properties of melphalan are listed in the following table.

Property	Information
Molecular weight	305.2 ^a
Melting point	182°C to 183°C (decomposes) ^a
Log <i>K</i> _{ow}	-0.52 (at pH 7) ^a
Water solubility	0.0457 g/L at 25°C ^b
Vapor pressure	3 × 10 ⁻¹⁰ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Melphalan is used as a drug to treat cancer and other medical conditions, including ovarian cancer, malignant melanoma, multiple myeloma (bone-marrow cancer), breast cancer, advanced prostate cancer, testicular cancer (seminoma), chronic myelogenous leukemia, osteogenic sarcoma (childhood bone cancer), polycythemia vera (overproliferation of blood cells), amyloidosis (accumulation of amyloid protein in tissues), and scleromyxedema (a rare skin disease). It is also used as an insect chemosterilant (IARC 1975, HSDB 2009, MedlinePlus 2009).

Production

In 2009, melphalan was produced by one U.S. manufacturer (HSDB 2009) and was available from 11 U.S. suppliers (ChemSources 2009), and drug products approved by the U.S. Food and Drug Administration containing melphalan as the active ingredient were produced by one U.S. pharmaceutical company (FDA 2009). Imports of melphalan totaled 165 kg (364 lb) in 1983 (HSDB 2009). No other data on U.S. imports or exports of melphalan were found.

Exposure

The general population is not expected to be exposed to melphalan, because its use is limited to medical treatment. Melphalan is available in 2-mg tablets and in an injectable form (melphalan hydrochloride, in 50-mg vials) (FDA 2009). The usual oral dose is 6 mg daily for two to three weeks, followed by a rest period of about four weeks. Maintenance therapy is usually 2 to 4 mg per day. For intravenous therapy, the usual dose is 16 mg/m² infused over 15 to 20 minutes, repeated at two-week intervals for four doses and then at four-week intervals (Chabner *et al.* 2001). In 2009, 428 clinical trials involving melphalan were in progress or recently completed (ClinicalTrials 2009).

Health professionals who handle melphalan, such as pharmacists, nurses, and physicians, could potentially be exposed during drug preparation, administration, or cleanup; however, exposure can be avoided through use of appropriate containment equipment and work practices (Zimmerman *et al.* 1981). One study reported that exposure of hospital personnel to melphalan could be reduced by treating excess solutions, spills, and urinals with chlorine bleach (Hansel *et al.* 1997). Occupational exposure also may occur during drug formulation or packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,418 workers, including 974 women, potentially were exposed to melphalan (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of melphalan = U150.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Melphalan is a prescription drug subject to specific labeling requirements.

Guidelines**National Institute for Occupational Safety and Health (NIOSH)**

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Methoxsalen with Ultraviolet A Therapy

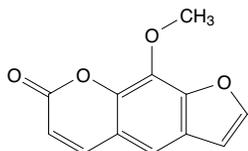
CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Methoxsalen is also known as 8-methoxypsoralen (CAS No. 298-81-7)

Methoxsalen with ultraviolet A therapy is also known as PUVA

**Carcinogenicity**

Methoxsalen (psoralen) with ultraviolet A (UVA) long-wave therapy (PUVA) is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

A cohort study of 1,380 psoriasis patients treated with PUVA found that the risk of skin cancer (squamous-cell carcinoma) increased with increasing exposure to PUVA; exposure to high doses of PUVA increased the risk of cancer by more than 50-fold. The risk was independent of any possible confounding by treatment with ionizing radiation or coal tar. An association between basal-cell carcinoma and PUVA exposure also was observed; however, the estimated risk at high exposure was fourfold lower than that observed for squamous-cell carcinoma. Increased risks of skin cancer were not reported in two smaller cohort studies; one study included only 94 patients, and the other used a low dose and may not have had sufficient statistical power to detect an effect. A case-control study also reported an increased risk of skin cancer among psoriasis patients treated with PUVA. Supporting the association between skin cancer and PUVA exposure are several case reports of skin cancer (basal-cell and squamous-cell carcinoma and malignant melanoma) in patients treated with PUVA for psoriasis or mycosis fungoides (a form of lymphoma primarily affecting the skin). In two small randomized clinical trials evaluating whether methoxsalen would protect against sunlight-induced skin cancer (by increasing pigmentation and cornification of the skin), methoxsalen administered alone for over two years did not affect the incidence of skin cancer (IARC 1980, 1982, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of PUVA from studies in experimental animals. Methoxsalen administered in the diet, by intraperitoneal injection, or by dermal application in combination with ultraviolet light caused benign and malignant epidermal and dermal skin tumors in mice. These included epidermal papilloma and carcinoma, squamous-cell carcinoma, fibrosarcoma, lymphosarcoma, basal-cell carcinoma, and hemangioma. Some squamous-cell and basal-cell carcinomas metastasized. Malignant tumors of the ears and the eye region (epidermal fibrosarcoma and squamous-cell carcinoma) were observed in female mice following intraperitoneal administration of methoxsalen and exposure to ultraviolet light (IARC 1980, 1987).

Studies on Mechanisms of Carcinogenesis

Methoxsalen readily absorbs ultraviolet light, particularly UVA wavelengths (320 to 400 nm). As a photosensitizing agent, it can produce phototoxic erythema (a reaction similar to sunburn) when skin to which it has been applied receives excess exposure to UVA. Chronic reactions may result in hyperpigmentation and skin thickening. UVA causes a photochemical reaction that results formation of adducts between methoxsalen and the pyrimidine bases of DNA (Rice and Cohen 1996).

Properties

Methoxsalen belongs to a group of drugs known as psoralen derivatives and exists as white to cream-colored fluffy crystals at room temperature (NTP 1989). It is practically insoluble in water, sparingly soluble in ether and liquid petrolatum, soluble in boiling alcohol, acetone, benzene, acetic acid, fixed vegetable oils, and propylene glycol, and freely soluble in chloroform. Methoxsalen is easily hydrolyzed and is unstable in the presence of air and light (Akron 2009). Physical and chemical properties of methoxsalen are listed in the following table. (For properties of ultraviolet radiation, see the profile for Ultraviolet Radiation Related Exposures.)

Property	Information
Molecular weight	216.2 ^a
Density	1.539 g/cm ^{3b}
Melting point	148°C ^a
Boiling point	415°C ^b
Log <i>K</i> _{ow}	2.14 ^c
Water solubility	0.0476 g/L at 30°C ^c
Vapor pressure	4 × 10 ⁻⁷ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Psoralen-containing plant extracts were first used in photochemotherapy to treat vitiligo in Egypt and India as far back as 1500 B.C. The acronym PUVA was coined in 1974 following successful treatment of severe psoriasis with 8-methoxypsoralen and UVA. Methoxsalen is now used in combination with UVA in the treatment of vitiligo, severe psoriasis, atopic dermatitis, alopecia areata, lichen planus, urticaria pigmentosa, cutaneous T-cell lymphoma, and some forms of photosensitivity (Wyatt *et al.* 2001).

Topical, bath, oral, and extracorporeal (outside the body) treatments are available by prescription only. To treat vitiligo, the topical solution is applied to the affected area and allowed to dry for several minutes before a second application, and the treated area is exposed to UVA about 2 hours later. For bath treatment of small areas (e.g., hands and feet), the area to be treated is soaked in a dilute solution of methoxsalen for 30 minutes and then immediately exposed to UVA. Oral preparations include hard and soft gelatin capsules for treatment of mycosis fungoides, psoriasis, and vitiligo; they may be given two or three times per week with at least 48 hours between doses. Methoxsalen also is used along with UVA to treat white blood cells to control skin problems caused by cutaneous T-cell lymphoma, a cancer of the lymphatic system. The white blood cells are removed from the blood, treated in a process called “photopheresis,” and returned to the body (LLS 2006).

Production

Methoxsalen is produced naturally by several plants (e.g., limes, celery, figs, and parsnips) found in both temperate and tropical regions (Drugge and Dunn 2003). It was first marketed in the United States in 1955. In 1980, one U.S. company reportedly produced the chemical, but no production data were available (IARC 1980). In 2009, no U.S. producers of methoxsalen were identified (SRI 2009), but it was available from 14 U.S. suppliers (ChemSources 2009), and four drug products approved by the U.S. Food and Drug Administration containing methoxsalen as the active ingredient were produced by two U.S. pharmaceutical companies (FDA 2009).

Exposure

The primary routes of human exposure to methoxsalen are dermal contact and ingestion. Individuals with skin diseases may be exposed to PUVA during treatment. Methoxsalen rapidly penetrates the epidermis and dermis upon contact with the skin. For medicinal effectiveness, both oral and topical administration require subsequent exposure to UVA (at 320 to 400 nm). Methoxsalen formulations are available in 10-mg capsules (hard and soft), 1% topical solutions, and 0.02 mg/mL injectable solutions (FDA 2009). The oral dosage (for adults and children aged 12 years or older) is 0.4 to 0.6 mg/kg of body weight, given 1.5 to 4 hours before UVA exposure (Wyatt *et al.* 2001). Because of differences in phototoxic response, the initial UVA dose must be determined for each individual. Under one protocol, the initial UVA dose is based on an individual's minimal phototoxic dose (the dose that when given with the appropriate dose of methox-

salen produces erythema), which is determined by exposing small areas of the thigh to UVA doses increasing from 0.5 to 9 J/cm². Alternatively, the initial UVA dose is based on the patient's skin type; patients with fairer skin that burns easily receive lower doses than those with darker skin that is less prone to burn. Following the initial dose, therapy usually is repeated two to four times per week, and the UVA dose is increased by 0.5 to 2.0 J/cm² per treatment. Generally, the dose of methoxsalen is not increased during treatment (Kostović *et al.* 2002). No information was found regarding the number of people treated with PUVA therapy.

Occupational exposure to methoxsalen may occur during preparation, formulation, administration, or application of the pharmaceutical products. Individuals occupationally exposed to methoxsalen may also be exposed to ultraviolet light during therapy or during subsequent exposure to sunlight.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

PUVA is regulated as a prescription drug or therapy.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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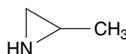
2-Methylaziridine

CAS No. 75-55-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as propylenimine



Carcinogenicity

2-Methylaziridine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2-methylaziridine caused tumors at several different tissue sites in rats. Administration of 2-methylaziridine by stomach tube for 28 or 60 weeks caused mainly mammary-gland cancer in females and leukemia in males. Increased incidences were also reported for cancer of the central nervous system (glioma) and ear canal (squamous-cell carcinoma) in both sexes and of the intestine (adenocarcinoma) in males (IARC 1975, 1999, Weisburger *et al.* 1981).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 2-methylaziridine.

Properties

2-Methylaziridine is the simplest heterocyclic amine and is a reactive alkylating agent (IARC 1999). It exists at room temperature as a colorless oily liquid with an ammonia-like odor and is miscible with water and soluble in ethanol and most organic solvents (Akron 2009, HSDB 2009). 2-Methylaziridine undergoes violent polymerization on contact with acids or acid vapors and may explode. Physical and chemical properties of 2-methylaziridine are listed in the following table.

Property	Information
Molecular weight	57.1 ^a
Specific gravity	0.812 at 16°C/4°C ^a
Melting point	-65°C ^a
Boiling point	66°C to 67°C at 760 mm Hg ^a
Log K_{ow}	0.13 ^b
Water solubility	1,000 g/L ^b
Vapor pressure	112 mm Hg at 20°C ^b
Vapor density relative to air	2 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

2-Methylaziridine is used in the United States exclusively as a chemical intermediate, and its derivatives are used in the paper, textile, rubber, and pharmaceutical industries (IARC 1975, HSDB 2009). Because it easily forms imines, its primary use is in the modification of latex surface-coating resins to improve adhesion. Because of the substantive bonding of imines to cellulose derivatives, polymers modified with 2-methylaziridine or its derivatives have been used in the adhesive, textile, and paper industries. 2-Methylaziridine has been used to modify dyes for specific adhesion to cellulose, and derivatives have been used in photography, gelatins, and synthetic resins. In the

oil-additive industry, 2-methylaziridine and its derivatives have been used as modifiers for viscosity control, high-pressure performance, and oxidation resistance. Other applications include use in flocculants in petroleum refining, as a modifier for rocket propellant fuels, in fiber modification, and in imine derivatives for use in medicinal and agricultural chemicals.

Production

In 2009, 2 methylaziridine was produced by one manufacturer in the United States and one in Europe (SRI 2009) and was available from nine suppliers, including six U.S. suppliers (ChemSources 2009). U.S. production of 2 methylaziridine was at least 100,000 lb in 1977, but had fallen to 5,000 lb by 1982 (HSDB 2009). Reports filed from 1986 through 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 2 methylaziridine totaled 10,000 to 500,000 lb (EPA 2004). No other data on U.S. production, imports, or exports of 2 methylaziridine were found.

Exposure

The primary routes of potential human exposure to 2-methylaziridine are inhalation, ingestion, and dermal contact (HSDB 2009). According to EPA's Toxics Release Inventory, environmental releases of 2-methylaziridine between 1988 and 2009 ranged from a low of 89 lb in 2000 to a high of 1,482 lb in 2009. Nearly all of the releases have been to air, with small quantities (~5 lb per year) released to surface water or off-site landfills. In 2007, three facilities released a total of 1,482 lb (TRI 2009). If released to air, 2-methylaziridine is expected to exist in the vapor phase and can react with photochemically generated hydroxyl radicals, with a half-life of 1.6 days (HSDB 2009). If released to surface water or moist soil, it is expected to hydrolyze, with a half-life of 17.5 days. Although it can be mobile in soil, 2-methylaziridine does not leach into groundwater, because it degrades very rapidly. It may also volatilize relatively slowly from wet soil or surface water but relatively rapidly from dry soil.

Because of its volatility, occupational exposure could occur during production, packaging, or use of substances made with 2-methylaziridine (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 20 workers potentially were exposed to 2-methylaziridine in 1974 (HSDB 2009). The American Conference of Governmental Industrial Hygienists noted the potential for dermal exposure, including via the mucous membranes and eyes, by airborne or direct contact and have given 2-methylaziridine a skin designation (ACGIH 2009).

Regulations

Department of Transportation (DOT)

2-Methylaziridine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 1 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-methylaziridine = P067.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 2 ppm (5 mg/m³).

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 ppm (0.5 mg/m³)
Threshold limit value – short-term exposure limit (TLV-STEL) = 0.4 ppm (1 mg/m³)

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 2 ppm (5 mg/m³).
Immediately dangerous to life and health (IDLH) limit = 100 ppm (250 mg/m³).
Listed as a potential occupational carcinogen.

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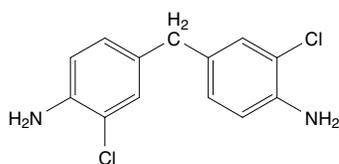
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4,4'-Methylenebis(2-chloroaniline)**CAS No. 101-14-4**

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as methylene-bis-*ortho*-chloroaniline, MBOCA, or MOCA

**Carcinogenicity**

4,4'-Methylenebis(2-chloroaniline) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4,4'-Methylenebis(2-chloroaniline) caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary administration of 4,4'-methylenebis(2-chloroaniline) caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats of both sexes and in female mice (IARC

1974). Dietary exposure also caused malignant blood-vessel tumors (hemangiosarcoma) in mice of both sexes, benign and malignant lung tumors (adenoma and adenocarcinoma) in rats of both sexes, and mammary-gland cancer (adenocarcinoma) in female rats. Cancer of the liver (hepatocellular carcinoma) and lung (carcinoma) also were observed in rats (sex not specified) administered 4,4'-methylenebis(2-chloroaniline) by subcutaneous injection.

Since 4,4'-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens*, additional studies in experimental animals have been identified. Dietary administration of 4,4'-methylenebis(2-chloroaniline) to male rats caused cancer of the Zymbal gland (carcinoma) and mammary gland (adenocarcinoma), in addition to liver and lung tumors as reported in earlier studies (Kommineneni *et al.* 1979). In female dogs, administration of 4,4'-methylenebis(2-chloroaniline) in capsule form caused cancer of the urinary bladder (transitional-cell carcinoma) and urethra (mixed transitional-cell carcinoma and adenocarcinoma) (Stula *et al.* 1978).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 4,4'-methylenebis(2-chloroaniline). Since 4,4'-methylenebis(2-chloroaniline) was listed in the *Third Annual Report on Carcinogens*, additional studies in humans have been identified. In studies of workers exposed to 4,4'-methylenebis(2-chloroaniline) in the United States and Taiwan, cases of urinary-bladder cancer were detected in a screening program; however, expected rates of asymptomatic urinary-bladder cancer were not available for comparison (IARC 1993, Chen *et al.* 2005). In a small U.K. cohort of male 4,4'-methylenebis(2-chloroaniline) production workers, one urinary-bladder cancer death was reported, yielding a statistically nonsignificant fivefold increase in mortality and threefold increase in incidence, compared with national rates (Dost *et al.* 2009).

Properties

4,4'-Methylenebis(2-chloroaniline) is a chlorinated aromatic amine that exists at room temperature as a tan to colorless crystalline solid with a faint amine odor (IARC 1993, Akron 2009, HSDB 2010). It is practically insoluble in water; soluble in oxygenated solvents, trichloroethylene, toluene, ethoxyethyl acetate, methyl ethyl ketone, tetrahydrofuran, acetone, esters, aromatic hydrocarbons, dimethyl sulfoxide, dimethyl formamide, dilute acids, and carbon tetrachloride; and very soluble in benzene, diethyl ether, and ethanol. When heated to over 200°C, 4,4'-methylenebis(2-chloroaniline) undergoes an exothermic and self-sustaining decomposition reaction, which in a closed container can cause an explosion (Akron 2009). Physical and chemical properties of 4,4'-methylenebis(2-chloroaniline) are listed in the following table.

Property	Information
Molecular weight	267.0 ^a
Specific gravity	1.44 ^a
Melting point	110°C ^a
Boiling point	378.9°C ^b
Log <i>K</i> _{ow}	3.91 ^a
Water solubility	13.9 mg/L at 24°C ^b
Vapor pressure	2.86 × 10 ⁻⁷ mm Hg at 25°C ^a

Sources: ^aHSDB 2010, ^bChemID Plus 2009.

Use

4,4'-Methylenebis(2-chloroaniline) has been used primarily as a curing agent for isocyanate polymers and polyurethane prepolymers in the manufacture of castable urethane rubber products such as indus-

trial tires and rollers, shock-absorption pads, and conveyor belting (IARC 1993, HSDB 2010). It is also used as a curing agent for epoxy. The cured polymers have many uses, including the manufacture of gun mounts, jet engine turbine blades, radar systems, and components in home appliances. In the laboratory, 4,4'-methylenebis(2-chloroaniline) has been used as a positive control for studying mutagens and carcinogens (HSDB 2010).

Production

Production of 4,4'-methylenebis(2-chloroaniline) was first reported in the United States in 1956 (IARC 1974). In 2010, 4,4'-methylenebis(2-chloroaniline) was produced by three manufacturers in east Asia, one manufacturer each in China and Europe, and none in the United States (SRI 2010) and was available from 24 suppliers, including 12 U.S. suppliers (ChemSources 2010). U.S. imports of 4,4'-methylenebis(2-chloroaniline) totaled over 1.9 million pounds in 1989 (HSDB 2010) and almost 2.0 million pounds in 1991 (ATSDR 1994). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenebis(2-chloroaniline) totaled between 1 million to 10 million pounds from 1986 to 1998, falling to between 500,000 lb and 1 million pounds in 2002 and 2006 (EPA 2004, 2009).

Exposure

The primary route of potential human exposure to 4,4'-methylenebis(2-chloroaniline) is dermal contact; other potential routes are inhalation and ingestion (IARC 1993). According to EPA's Toxics Release Inventory, environmental releases of 4,4'-methylenebis(2-chloroaniline) since 1988 have ranged from lows of 19 lb in 1992 and 26 lb in 1998 to highs of 14,933 lb in 1993 and 26,185 lb in 2000. Releases fell to 14,719 lb in 2001 and 1,708 lb in 2002, remaining around 2,000 lb from 2002 to 2004. Most releases before 1999 were to air; since then, most releases have been to land. In 2005, 5,000 lb of 4,4'-methylenebis(2-chloroaniline) was released to air and to off-site landfills. The release total and pattern remained similar through 2007, when five facilities released a total of 6,233 lb (TRI 2010). 4,4'-Methylenebis(2-chloroaniline) has been identified in at least four hazardous-waste sites on the National Priorities List (ATSDR 1994).

When released to air, 4,4'-methylenebis(2-chloroaniline) will exist mainly as a particulate that is removed by dry and wet deposition; the portion that remains in the vapor phase will react with hydroxyl radicals, with a half-life of 5 hours. If released to surface water, 4,4'-methylenebis(2-chloroaniline) is likely to be strongly adsorbed to organic matter or may be photodegraded in surface water, but is not easily hydrolyzed. If released to soil, it will bind to soil particles and will have slight mobility in the subsurface environment; however, it may be subject to aerobic biodegradation. It may bioaccumulate in food plants but is not readily translocated through the plant (ATSDR 1994, HSDB 2010).

In 1979, 4,4'-methylenebis(2-chloroaniline) was detected in soil samples obtained within a 1-km (0.6-mi) radius of a chemical plant in Michigan; concentrations in soil samples from along public roads in the area were as high as 590 ppm. Concentrations of 4,4'-methylenebis(2-chloroaniline) were as high as 18 ppm in sludge from the wastewater-treatment plant in the area and over 1,600 ppm in sediment from an on-site industrial lagoon (ATSDR 1994).

The risk of exposure to 4,4'-methylenebis(2-chloroaniline) is greatest for workers involved in the manufacture of polyurethane and plastic products where 4,4'-methylenebis(2-chloroaniline) is used as a curing agent (ATSDR 1994). When used for this purpose, 4,4'-methylenebis(2-chloroaniline) is melted before being mixed

into an elastomer formulation; it potentially could volatilize and be emitted into waste gases and wastewater (IARC 1993, ATSDR 1994, TRI 2010). Urine from workers at polyurethane plastics manufacturing facilities in the United Kingdom, France, and Australia contained 4,4'-methylenebis(2-chloroaniline) at concentrations as high as 1.3 mg/L of urine (IARC 1993, ATSDR 1994, Vaughan and Kenyon 1996, Robert *et al.* 1999a,b). In 2006, the U.S. Occupational Safety and Health Administration conducted an occupational exposure investigation of a small U.S. company that manufactured pliable polyurethane parts. Surface wipe samples collected from the top of the metal scale table were reported to have concentrations of 4,4'-methylenebis(2-chloroaniline) as high as 209 µg/m², and total 4,4'-methylenebis(2-chloroaniline) was measured in the urine of one worker at a concentration of 15 µg/L (Fairfax and Porter 2006). In a manufacturing facility in Taiwan, 4,4'-methylenebis(2-chloroaniline) was found in the air at concentrations of up to 0.41 mg/m³ (410 µg/m³) (Chen *et al.* 2005), and concentrations in the urine of 10 workers ranged from 267.9 to 15,701.1 µg/g of creatinine (mean = 5,544 µg/g) (Liu *et al.* 2005).

Regulations

Department of Transportation (DOT)

4,4'-Methylenebis(2-chloroaniline) is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 4,4'-methylenebis(2-chloroaniline) = U158.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

4,4'-Methylenebis(2-chloroaniline) is prohibited from indirect addition to human food through food-contact surfaces; food containing any added or detectable level of this substance is prohibited.

4,4'-Methylenebis(2-chloroaniline) may be used as antioxidants and/or stabilizers for polymers in indirect food additives as prescribed in 21 CFR 178.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.01 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.003 mg/m³.

Listed as a potential occupational carcinogen.

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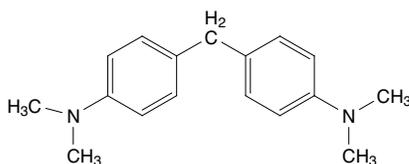
4,4'-Methylenebis(N,N-dimethyl)benzenamine

CAS No. 101-61-1

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as Michler's base or or *p,p'*-tetramethyldiaminodiphenylmethane



Carcinogenicity

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4'-methylenebis(*N,N*-dimethyl)benzenamine caused tumors in two rodent species and at two different tissue sites. Dietary administration of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine caused cancer of the thyroid gland (follicular-cell carcinoma) in rats of both sexes and increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female mice (NCI 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-methylenebis(*N,N*-dimethyl)benzenamine.

Properties

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine is a bicyclic aromatic amine that exists at room temperature as yellowish glistening leaflets or plates or as tan crystals with a faint odor (NCI 1979, Akron 2009, HSDB 2009). Commonly referred to as Michler's base, it is the reduced form of Michler's ketone, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. 4,4'-Methylenebis(*N,N*-dimethyl)benzenamine is practically insoluble in water, slightly soluble in cold alcohol, and soluble in hot alcohol, benzene, diethyl ether, carbon disulfide, and acids (ChemIDplus 2009, HSDB 2009). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine are listed in the following table.

Property	Information
Molecular weight	254.4 ^a
Density	1.14 g/cm ³ at 20°C ^b
Melting point	90°C to 91°C ^a
Boiling point	390°C ^a
Log <i>K</i> _{ow}	4.37 ^c
Water solubility	4.14 mg/L at 25°C ^c
Vapor pressure	1.75 × 10 ⁻⁵ mm Hg at 25°C ^c
Vapor density relative to air	8.77 ^b

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

4,4'-Methylenebis(*N,N*-dimethyl)benzenamine is used as an intermediate in the manufacture of at least six dyes and one pigment (including methylene red and C.I. basic yellow 2, basic orange 14, solvent orange 15, and solvent yellow 34). Its hydrochloride salt is used as an analytical reagent for the determination of lead (IARC 1982).

Production

Commercial production of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine in the United States began in the early 1920s (IARC 1982). U.S. production was approximately 1.8 million pounds in 1974, decreasing to 1.0 million pounds in 1977. In 2009, 4,4'-methylenebis(*N,N*-dimethyl)benzenamine was produced by one manufacturer each in China, Europe, and India (SRI 2009) and was available from 16 suppliers, including 10 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenebis(*N,N*-dimethyl)benzenamine totaled 500,000 lb to 1 million pounds in 1986 and 10,000 to 500,000 lb in 1990 (EPA 2004); no inventory update reports for 4,4'-methylenebis(*N,N*-dimethyl)benzenamine were filed in 1994, 1998, or 2002.

Exposure

The routes of potential human exposure to 4,4'-methylenebis(*N,N*-dimethyl)benzenamine are inhalation, ingestion, and dermal contact (NJDHSS 2009). EPA's Toxics Release Inventory reported environmental releases of 8,400 lb in 1988, 10 lb in 1995, and 1 lb in 1996; no more recent releases have been reported (TRI 2009). Although the compound is relatively nonvolatile, workers may be exposed via inhalation of dust. The potential for exposure is greatest among workers in the dye and chemical manufacturing industries (NCI 1979).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 4,140 workers potentially were exposed to 4,4'-methylenebis(*N,N*-dimethyl)benzenamine (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

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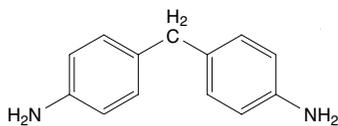
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4,4'-Methylenedianiline and Its Dihydrochloride

CAS Nos. 101-77-9 and 13552-44-8

Reasonably anticipated to be human carcinogens

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

4,4'-Methylenedianiline and its dihydrochloride salt are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4'-methylenedianiline dihydrochloride caused tumors at several different tissue sites in mice and rats. Administration of 4,4'-methylenedianiline dihydrochloride in the drinking water caused benign and/or malignant tumors of the thyroid gland (C-cell adenoma or follicular-cell adenoma or carcinoma) in mice and rats of both sexes and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and in male rats.

It also caused malignant lymphoma in female mice and benign adrenal-gland tumors (pheochromocytoma) in male mice (NTP 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-methylenedianiline or its dihydrochloride.

Properties

4,4'-Methylenedianiline is an aromatic amine that exists at room temperature as colorless to pale yellow to tan flakes or lumps with a faint amine-like odor (IARC 1986, Akron 2009, HSDB 2009). 4,4'-Methylenedianiline is only slightly soluble in water, but soluble in ethanol, benzene, diethyl ether, and acetone. The dihydrochloride salt is soluble in water. 4,4'-Methylenedianiline is stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4'-methylenedianiline are listed in the following table.

Property	Information
Molecular weight	198.3 ^a
Specific gravity	1.056 at 100°C/4°C ^a
Melting point	91.5°C to 92°C ^a
Boiling point	398°C to 399°C at 768 mm Hg ^a
Log <i>K</i> _{ow}	1.59 ^a
Water solubility	1 g/L at 25°C ^b
Vapor pressure	1 mm Hg at 197°C ^a
Vapor density relative to air	6.8 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

More than 90% of the 4,4'-methylenedianiline produced in the United States is used as a chemical intermediate in the closed-system production of 4,4'-methylenedianiline diisocyanate and polyisocyanates (NTP 1983, IARC 1986). These products are used to produce a variety of polymers and resins, such as polyurethane foam, elastomers (e.g., Spandex fibers), and isocyanate resins. 4,4'-Methylenedianiline is also used as a cross-linking agent for epoxy resins, and the U.S. Food and Drug Administration has approved the use of these epoxy resins to coat containers for beverages having an alcohol content of up to 8%. 4,4'-Methylenedianiline is also used as an analytical reagent for analysis, including the determination of tungsten and sulfates, as a corrosion inhibitor, as an antioxidant and curative agent in rubber, and to prepare azo dyes (IARC 1986, ATSDR 1998). No data were available on the use of the dihydrochloride salt.

Production

4,4'-Methylenedianiline has been produced commercially in the United States since the early 1920s (IARC 1986). It is available in bulk quantities containing approximately 96% 4,4'-methylenedianiline, 3% other isomeric amines, and traces of aniline (ATSDR 1998). In the early 1980s, six or seven manufacturers produced between 200 million and 400 million pounds of 4,4'-methylenedianiline per year. In 1987, about 600 million pounds was produced and used captively as a chemical intermediate, 4.5 million pounds was produced domestically for sale, and 1.8 million pounds was imported (OSHA 1987). In 2009, 4,4'-methylenedianiline was produced by ten manufacturers worldwide, including one in the United States (SRI 2009), and was available from 28 suppliers, including 14 U.S. suppliers (ChemSources 2009). No producers or suppliers of the hydrochloride salt were identified. From 1989 to 1993, U.S. imports of 4,4'-methylenedianiline were 3.3, 2.9, 2.4, 2.0, and 1.1 million pounds, and U.S. exports were 28.9, 29.8, 12.8, 15.7, and 9.9 million pounds (ATSDR 1998). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Con-

tol Act Inventory Update Rule indicated that U.S. production plus imports of 4,4'-methylenedianiline totaled 100 million to 500 million pounds in 1986, falling to between 1 million and 10 million pounds in 1990, remaining in that range in through 2002 (EPA 2004), and returning to between 100 million and 500 million pounds in 2006 (EPA 2009). No data on U.S. production, imports, or exports of the dihydrochloride salt were found.

Exposure

Although most exposure to 4,4'-methylenedianiline is occupational, the general population may be exposed through dermal contact with trace amounts present in consumer products made from polyurethane foam, Spandex, and epoxy-containing products. Although 4,4'-methylenedianiline may be used in their production, very little of the chemical is present in its free state in the final products. Levels of 4,4'-methylenedianiline in food and food packaging are so low that exposure is unlikely. Polyurethane is used in medical devices, and exposure may occur from small releases of 4,4'-methylenedianiline during sterilization with gamma radiation; patients most likely to be exposed from this source are those receiving frequent blood transfusions or undergoing kidney dialysis (ATSDR 1998).

4,4'-Methylenedianiline may be released to the environment during industrial production and use (IARC 1986, ATSDR 1998). Very few data were available regarding concentrations of 4,4'-methylenedianiline in ambient air, surface water, industrial effluents, or soil. According to EPA's Toxics Release Inventory, environmental releases of 4,4'-methylenedianiline declined from 736,000 lb in 1988 to 29,000 lb in 1992 and remained between 29,000 and 78,000 lb through 2003. Releases increased in 2004, reaching 207,176 lb in 2005, and then decreased, reaching 67,423 lb in 2007. In 2007, 58,000 lb of 4,4'-methylenedianiline was released from one facility to an underground injection well, and most of the remainder was released to air. Reporting is not required for the hydrochloride salt (TRI 2009). If 4,4'-methylenedianiline is released to air, the vapor phase will be degraded by photochemically produced hydroxyl radicals, with a half-life of 1.6 hours (HSDB 2009). If released to soil, 4,4'-methylenedianiline will covalently bind to humic material, but will leach from soil without humic material. If released to water, 4,4'-methylenedianiline may covalently bind to suspended solids and sediments containing humic material. On the water surface, it will be susceptible to degradation by photochemically produced hydroxyl and peroxy radicals, with a half-life of 19 to 30 hours.

The primary routes of potential occupational exposure to 4,4'-methylenedianiline are inhalation and dermal contact. Workers may be exposed while producing, formulating, and packaging the chemical, during its use, and from hydrolysis of 4,4'-methylenedianiline diisocyanate. No 4,4'-methylenedianiline is released during autoclave sterilization of medical equipment (IARC 1986, ATSDR 1998). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that over 15,000 workers, including about 3,400 women, potentially were exposed to 4,4'-methylenedianiline (NIOSH 1990). In 1992, the Occupational Safety and Health Administration estimated that 3,836 workers in 11 principal industry sectors were exposed to 4,4'-methylenedianiline (OSHA 1992), at air concentrations ranging from 1 to 250 ppb and for average annual exposure durations of 47 to 250 days. 4,4'-Methylenedianiline was measured at concentrations of up to 31 mg/m³ in air inside facilities where it was produced and up to 1.6 mg/m³ inside fabrication facilities while it was being used. It was detected in the urine of 4 of 27 production workers (14.9%) at concentrations of at least 200 µg/L in 1970, but in the urine of only 0.09% of workers (numbers not reported) at concentrations of 20 µg/L or less in 1980 (IARC 1986, ATSDR 1998). In a

2005 risk assessment, the concentration of 4,4'-methylenedianiline in freshly produced polyurethane foam was 2 to 3.5 mg/kg at the time of demolding, declining to 1 mg/kg one hour after demolding and continuing to decline slowly over time (Lewandowski *et al.* 2005); based on these concentrations, cancer risks from dermal exposure were found to be below the level of concern. It was assumed that adequate ventilation would minimize inhalation exposure.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 4,4'-Methylenedianiline is listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of 4,4'-methylenedianiline is subject to certain provisions for the control of volatile organic compound emissions.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb for 4,4'-methylenedianiline.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: 4,4'-Methylenedianiline is a listed substance subject to reporting requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.010 ppm for 4,4'-methylenedianiline. Short-term exposure limit (STEL) = 0.10 ppm for 4,4'-methylenedianiline. Comprehensive standards have been developed for occupational exposure to 4,4'-methylenedianiline and its salts.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 ppm for 4,4'-methylenedianiline.

National Institute for Occupational Safety and Health (NIOSH)

4,4'-Methylenedianiline is listed as a potential occupational carcinogen.

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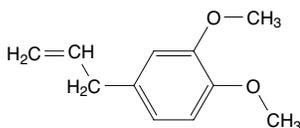
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. <http://www.epa.gov/triexplorer> and select 4,4'-Methylenedianiline. Last accessed: 7/13/2009.

Methyleugenol

CAS No. 93-15-2

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Methyleugenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to methyleugenol caused tumors in two rodent species and at several different tissue sites. Methyleugenol administered by stomach tube caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats and mice of both sexes. In rats, methyleugenol also caused benign or malignant stomach tumors (neuroendocrine tumors) in both sexes and tumors of the kidney (renal-tubule adenoma), mammary gland (fibroadenoma), and skin (fibroma or fibrosarcoma) in males. Malignant neuroendocrine tumors of the stomach in male mice also were considered to be related to methyleugenol exposure (NTP 2000). Earlier studies found that methyleugenol and two structurally related allylbenzenes, safrole and estragole, caused liver tumors in mice when administered by intraperitoneal injection (IARC 1976, Miller *et al.* 1983). Safrole is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* and by the International Agency for Research on Cancer as possibly carcinogenic to humans.

Studies on Mechanisms of Carcinogenesis

Mechanistic studies indicate that liver tumors induced by methyleugenol and structurally related allylbenzenes result from metabolism of these compounds to DNA-reactive intermediates. Methyleugenol may be bioactivated by three different pathways: (1) hydroxylation at the 1' position of the allylic side chain to yield 1'-hydroxymethyleugenol, followed by sulfation of this intermediate to form 1'-hydroxymethyleugenol sulfate, (2) oxidation of the 2',3'-double bond of the allylic side chain to form methyleugenol-2,3-oxide, and (3) O-demethylation followed by spontaneous rearrangement to form eugenol quinone methide. Formation of protein adducts and DNA adducts in the livers of animals (and in cultured human hepatocytes) exposed to allylbenzenes and induction of liver tumors by these compounds in animals have been attributed to activation via the hydroxylation pathway, because similar effects were produced by the 1'-hydroxy metabolites and because these effects were inhibited by pretreatment with sulfotransferase inhibitors (Boberg *et al.* 1983, Miller *et al.* 1983, Randerath *et al.* 1984, Gardner *et al.* 1996, NTP 2000).

Methyleugenol, safrole, and estragole caused unscheduled DNA synthesis in rat hepatocytes, and their corresponding 1'-hydroxy metabolites were more potent genotoxic agents than were the parent compounds (Howes *et al.* 1990, Chan and Caldwell 1992). Methyleugenol caused morphological transformation of Syrian hamster

embryo cells (Kerckaert *et al.* 1996), sister chromatid exchange in Chinese hamster ovary (CHO) cells (NTP 2000), intrachromosomal recombination in yeast (Schiestl *et al.* 1989), and DNA repair in *Bacillus subtilis* (Sekizawa and Shibamoto 1982). It did not cause mutations in *Salmonella typhimurium* (NTP 2000) or *Escherichia coli* (Sekizawa and Shibamoto 1982), chromosomal aberrations in CHO cells (NTP 2000), or micronucleus formation in the peripheral-blood erythrocytes of mice (NTP 2000). A higher frequency of β -catenin mutations was observed in liver tumors from mice exposed to methyleugenol than in spontaneous liver tumors from unexposed mice (Devereux *et al.* 1999). Methyleugenol's lack of mutagenicity in bacteria may be due to the need for sulfation in the metabolic activation of methyleugenol to its ultimate mutagenic or carcinogenic form.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to methyleugenol.

Properties

Methyleugenol is an allyl-chain-substituted guaiacol that structurally resembles safrole (NTP 2000). It is a colorless to pale yellow, oily liquid with an odor of cloves and carnations. It is insoluble in water, glycol, and propylene glycol and soluble in ethanol, ethyl ether, chloroform, and many other organic solvents. Methyleugenol is unstable at room temperature; it darkens and thickens when exposed to air and readily evaporates at room temperature (NTP 2000). Physical and chemical properties of methyleugenol are listed in the following table.

Property	Information
Molecular weight	178.2 ^a
Specific gravity	1.0396 at 20°C/4°C ^a
Melting point	-4°C ^a
Boiling point	254.7°C at 760 mm Hg ^a
Log K_{ow}	3.03 ^b
Water solubility	0.500 g/L at 25°C ^b
Vapor pressure	1 mm Hg at 85.0°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Methyleugenol is used in fragrances and as a flavoring agent in jellies, baked goods, nonalcoholic beverages, chewing gum, candy, pudding, relish, and ice cream. It is also used as an insect attractant in combination with insecticides and has been used as an anesthetic in rodents (NTP 2000, HSDB 2009).

Production

Annual production of methyleugenol in the United States in 1990 was estimated at 25,000 lb (NTP 2000). No current production data were found.

Exposure

The general population may be exposed to methyleugenol through ingestion of foods or inhalation of fragrances containing the compound (HSDB 2009). Methyleugenol is a naturally occurring substance, present in many essential oils, including the oils of rose, pimento, basil, hyacinth, citronella, anise, nutmeg, mace, cinnamon leaves, pixuri seeds, and laurel fruits and leaves. It has also been found in blackberry essence, bananas, black pepper, and bilberries (NTP 2000). Methyleugenol is used in commercial products as a flavorant at concentrations of 5 to 52 ppm and in fragrances at concentrations of 0.002% to 0.3% (HSDB 2009). In a subset of serum samples from adults participating in the third National Health and Nutrition Examination

Survey, methyleugenol was detected in 98% of the 206 samples analyzed. The average methyleugenol concentration was 24 pg/g, and the highest concentration was 390 pg/g (Barr *et al.* 2000). Daily per-capita consumption of methyleugenol in food was estimated by the World Health Organization to be 0.073 mg (WHO 1981) and, more recently, 0.26 mg/kg of body weight (Stroffberg and Grundschober 1987, NAS 1989).

Although methyleugenol has been identified in various natural substances, no quantitative studies were found that assessed environmental (nondietary) exposure to methyleugenol. In air, methyl-eugenol exists as a vapor; it reacts with photochemically produced hydroxyl radicals and degrades with an estimated half-life of 5 hours (HSDB 2009). Methyleugenol has been detected in wastewater effluent from a paper mill (NTP 2000).

Occupational exposure to methyleugenol may occur through dermal contact, inhalation, and ingestion. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 12,682 workers, including 9,413 women, potentially were exposed to methyleugenol (NIOSH 1990).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to methyleugenol were identified.

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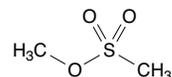
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Methyl Methanesulfonate

CAS No. 66-27-3

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)



Carcinogenicity

Methyl methanesulfonate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Methyl methanesulfonate caused tumors in mice and rats at several different tissue sites and by several different routes of exposure. Administration of methyl methanesulfonate in the drinking water caused benign lung tumors (adenoma) and lymphoma of the thymus in male mice. In male rats, subcutaneous injection of methyl methanesulfonate caused cancer at the injection site (squamous-cell carcinoma and polymorphic-cell sarcoma), and 1 of 12 rats developed kidney cancer (nephroblastoma). A single intraperitoneal injection of methyl methanesulfonate caused tumors of the nervous system (oligodendroglioma, malignant neurofibroma, astrocytoma, malignant neuroinoma, mixed glioma, or meningioma of the spinal cord) in adult rats of both sexes and in the offspring of pregnant rats exposed on gestation day 15 or 21 (Clapp *et al.* 1968, IARC 1974).

Since methyl methanesulfonate was listed in the *Sixth Annual Report on Carcinogens*, additional studies in rodents have been identified. In female mice, subcutaneous injection of methyl methanesulfonate caused cancer at the injection site (sarcoma) (Segal *et al.* 1987). In male rats exposed to methyl methanesulfonate by inhalation for six weeks and then observed for life, the incidence of nasal tumors (mainly squamous-cell carcinoma) was significantly increased (IARC 1999).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to methyl methanesulfonate.

Properties

Methyl methanesulfonate is an ester of sulfuric acid that exists as a colorless to amber liquid at room temperature. It is soluble in water, dimethyl formamide, and propylene glycol, but only slightly soluble in nonpolar solvents. Methyl methanesulfonate is stable under normal temperatures and pressures, but it forms irritating corrosive compounds or toxic gases in the presence of fire (IARC 1974, Akron 2009). Physical and chemical properties of methyl methanesulfonate are listed in the following table.

Property	Information
Molecular weight	110.1 ^a
Specific gravity	1.2943 at 20°C/4°C ^a
Melting point	20°C ^a
Boiling point	203°C at 753 mm Hg ^a
Log <i>K</i> _{ow}	-0.66 ^b
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	0.31 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Methyl methanesulfonate is used experimentally as a research chemical and as a solvent catalyst in polymerization, alkylation, and esterification reactions (IARC 1974, Wyatt and Pittman 2006, NIH 2007). It has been tested as a cancer chemotherapeutic agent, and the monoesters of methanesulfonic acid were considered for possible use as a reversible insect and mammalian pest chemosterilant and as a human male contraceptive (IARC 1974).

Production

Production of methyl methanesulfonate is limited, because it is used only in research (IARC 1974, 1999). Methyl methanesulfonate is not produced commercially in the United States (IARC 1999, HSDB 2009). In 2009, methyl methanesulfonate was available from 21 suppliers worldwide, including 13 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of methyl methanesulfonate were found.

Exposure

Exposure to methyl methanesulfonate appears to be limited to laboratory research personnel (IARC 1974, 1999). If released to air, methyl methanesulfonate will exist in the vapor phase and will react slowly with hydroxyl radicals, with a half-life of 69 days. If released to a moist environment, it will hydrolyze with a half-life of 4.56 hours at 25°C. It is not expected to bioconcentrate in aquatic organisms or volatilize from water (HSDB 2009).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

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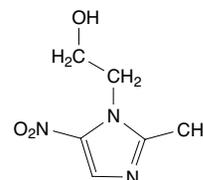
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Metronidazole

CAS No. 443-48-1

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Metronidazole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to metronidazole caused tumors at several different tissue sites in mice and rats. Dietary administration of metronidazole caused benign and malignant lung tumors (adenoma, adenocarcinoma, and carcinoma) in mice of both sexes, lymphoma in female mice (Rustia and Shubik 1972, IARC 1977), liver cancer (hepatocellular carcinoma) and mammary-gland tumors (fibroadenoma) in female rats, and tumors of the pituitary gland (adenoma) and testes (Leydig-cell tumors) in male rats (IARC 1982).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to metronidazole. An excess of cancer of the uterine cervix was found in two epidemiological studies of women treated with metronidazole for vaginal trichomoniasis (Beard *et al.* 1979, Friedman and Ury 1980, IARC 1982); however, trichomoniasis is a risk factor for cervical cancer, and one of the studies (Beard *et al.* 1979) showed a greater excess of cancer among women with trichomoniasis who were not exposed to metronidazole. The study by Beard *et al.*, but not that by Friedman *et al.*, reported an excess of lung cancer, which may have been due to smoking.

Since metronidazole was listed in the *Fourth Annual Report on Carcinogens*, additional epidemiological studies have been identified. In a follow-up of the cohort study by Beard *et al.*, the incidence of lung cancer (bronchogenic carcinoma) was significantly increased in women exposed to metronidazole, and the excess remained after an attempt to adjust for smoking (Beard *et al.* 1988). In a study of over 12,000 people who had used metronidazole, no excess of cancer (all tissue sites combined) was found after two and a half years of follow-up (IARC 1987). A large cohort study of cancer in children prenatally exposed to metronidazole found no overall excess of cancer (all tissue sites combined); a twofold increase in the risk of neuroblastoma (cancer of the sympathetic nervous system) was not statistically significant (Thapa *et al.* 1998).

Properties

Metronidazole is a nitroimidazole compound that exists at room temperature as white to pale-yellow crystals with a slight odor (Akron 2009). It is soluble in water, ethanol, ether, chloroform, and dilute acids and sparingly soluble in dimethylformamide (IARC 1977). It is stable under normal temperatures and pressure, but may discolor

upon exposure to light (Akron 2009). Physical and chemical properties of metronidazole are listed in the following table.

Property	Information
Molecular weight	171.2 ^a
Melting point	158°C to 160°C ^a
Log K_{ow}	-0.02 at 25°C ^a
Water solubility	10 g/L at 25°C ^b
Vapor pressure	3.05×10^{-7} mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bIARC 1977, ^cChemIDplus 2009.

Use

Metronidazole is used primarily as a drug for the treatment of infections by the parasitic protozoans *Entamoeba histolytica*, *Trichomonas vaginalis*, and *Giardia lamblia* (IARC 1977). It has also been used to treat Vincent's infection (trench mouth) and acne rosacea. It has been prescribed for invasive intestinal amoebiasis and amoebic hepatic abscess, antibiotic-associated colitis, balantidiasis, dental infection, gastritis or ulcer due to *Helicobacter pylori*, and inflammatory bowel disease (MedlinePlus 2009). It is also used as a trichomonacidal agent in veterinary medicine (IARC 1977, MedlinePlus 2009). Metronidazole may be administered orally (in capsules or tablets), vaginally (in creams, gels, or tablets), topically (in gels, creams, or lotions), or by intravenous injection (MedlinePlus 2009).

Production

Commercial production of metronidazole in the United States was first reported in 1963 (IARC 1977). In 1974, only one U.S. company reported producing metronidazole. In 1977, annual U.S. sales of metronidazole for medical use were estimated to be less than 28,600 lb. In 2009, metronidazole was available from 18 U.S. suppliers (Chem Sources 2009), and 42 drug products registered with the U.S. Food and Drug Administration contained metronidazole as an active ingredient (FDA 2009). No more recent data on U.S. production, imports, or exports were found.

Exposure

The primary routes of human exposure to metronidazole are ingestion, injection, or topical (including intravaginal) application for treatment of certain infectious diseases (MedlinePlus 2009). For treatment of bacterial infections, a recommended regimen is oral administration of 525 mg every 6 hours for seven days. As a systemic trichomonacidal agent, metronidazole typically is administered orally at a dosage of either 250 mg three times a day for seven days or 1 to 2 g twice on one day. When used to treat giardiasis, it is administered at 500 to 750 mg daily for five to ten days. For intravenous administration to treat bacterial infections, the typical regimen is 15 mg/kg of body weight initially, followed by 7.5 mg/kg every 6 hours for seven days. When administered prophylactically for colon surgery, metronidazole is injected 1 hour before surgery and at 6 and 12 hours after the first dose. When administered as a topical cream, it is usually applied twice a day for nine weeks. Metronidazole is also applied intravaginally either at 37.5 mg twice a day for five days for bacterial infections or 500 mg daily for 10 to 20 days for bacterial infections or trichomoniasis. In 2009, 149 clinical trials involving metronidazole were in progress or recently completed (ClinicalTrials 2009). Occupational exposure to metronidazole could occur through inhalation or dermal contact by workers involved in its manufacture, formulation, packaging, or administration.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Metronidazole is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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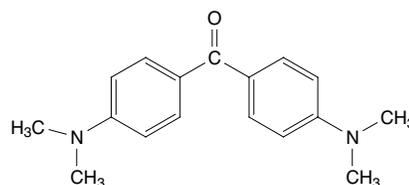
Michler's Ketone

CAS No. 90-94-8

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as 4,4'-(dimethylamino)benzophenone



Carcinogenicity

Michler's ketone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to Michler's ketone caused tumors in two rodent species and at two different tissue sites. Dietary administration of Michler's ketone caused liver cancer (hepatocellular carcinoma) in female mice and in rats of both sexes and blood-vessel cancer (hemangiosarcoma) in male mice (NCI 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to Michler's ketone.

Properties

Michler's ketone is a derivative of dimethylaniline and exists as white to green crystalline leaflets or blue powder at room temperature. Michler's ketone is practically insoluble in water, very soluble in pyrimidine, soluble in alcohol and warm benzene, and very slightly soluble in ether. It is stable under normal temperatures and pressures (NCI 1979, Akron 2009, HSDB 2009). Physical and chemical properties of Michler's ketone are listed in the following table.

Property	Information
Molecular weight	268.4 ^a
Melting point	172°C ^a
Boiling point	> 360°C decomposes ^a
Log K_{ow}	3.87 ^b
Water solubility	0.4 g/L at 20°C ^b
Vapor pressure	1.07×10^{-6} mm Hg at 25°C ^b
Dissociation constant (pK_a)	12.46 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Michler's ketone is a chemical intermediate used in the synthesis of at least 13 dyes and pigments, particularly auramine derivatives (NCI 1979, HSDB 2009). These pigments are used to make ultraviolet-cured printing ink for carton board and paper and as dyes for pen inks, carbon paper, alcoholic solvents, oils, waxes, textiles, and leather; one pigment is also used as a fungicide (Castle *et al.* 1997a,b, HSDB 2009).

Production

In 1975, U.S. production of Michler's ketone was estimated at over 908 kg (2,000 lb) (HSDB 2009). No current production data were found. In 2009, Michler's ketone was produced by one manufacturer in Europe (SRI 2009), and was available from 29 suppliers, including 16 U.S. suppliers (ChemSources 2009). U.S. imports of Michler's ketone totaled 548 kg (1,206 lb) in 1972, 20,000 kg (44,000 lb) in 1975 (HSDB 2009), and about 10,900 kg (24,000 lb) in 1983 (USITC 1984). No more recent data on U.S. imports or exports were found.

Exposure

The routes of potential human exposure to Michler's ketone are inhalation, ingestion, and dermal contact (Akron 2009). Michler's ketone may be present in some dyes used for printing and in minute quantities in final consumer products (Ozaki *et al.* 2004). Michler's ketone was measured in recycled paper and paperboard used in food packaging in Japan at concentrations of up to 12 µg/g. It was not detected in tested virgin paper or paperboard products. In another study, Michler's ketone was not detected in food that had been in contact with packaging containing Michler's ketone at a concentration of 3.9 µg/g (the highest concentration found in tested packaging) (Castle *et al.* 1997a). The U.S. Environmental Protection Agency's Toxics Release Inventory reported environmental releases of Michler's ketone of 1,100 lb in 1988 and 1,577 lb in 1995. In 1999, two indus-

trial facilities released 869 lb (TRI 2009). No release data have been reported since 1999.

The potential for occupational exposure is greatest for workers in facilities that manufacture Michler's ketone or any of the dyestuffs for which it is an intermediate (NCI 1979). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,026 workers, including 405 women, potentially were exposed to Michler's ketone (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act Toxics Release Inventory: Listed substance subject to reporting requirements.

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Mineral Oils: Untreated and Mildly Treated

CAS No.: none assigned

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Untreated and mildly treated mineral oils are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

The carcinogenicity of exposure to untreated and mildly treated mineral oils has been evaluated in numerous studies in a variety of occupations, including metal working, jute processing, mulespinning, newspaper press operation, and other newspaper work. Exposure to mineral oils was consistently and strongly associated with an increased risk of cancer of the scrotum and skin (squamous-cell carcinoma) for many occupations, including metal worker, mulespinner, and jute processor. An analysis of a series of 344 cases of scrotal cancer occurring from 1936 to 1976 in the West Midlands region of Eng-

land reported that 62% of the men had been exposed to mineral oils. Epidemiological studies (case-control, cohort, and proportional mortality studies) in metal workers have reported excesses of gastrointestinal, sinonasal, and bladder cancer, in addition to skin and scrotal cancer. Some but not all studies (case-control, cohort, and proportional mortality studies) of workers in the printing industry have reported significantly increased incidences of death from cancer of the lung, rectum, buccal cavity, and pharynx. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of untreated and mildly treated mineral oils in humans (IARC 1984, 1987)

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of some untreated and mildly treated mineral oils from studies in experimental animals. Evaluation of the carcinogenicity of mineral oils in experimental animals has mainly involved experiments in which petroleum-derived base oils and formulated products were applied repeatedly to the skin of mice; however, some types of mineral oil preparations were studied in other species and by other routes of exposure. Vacuum-distillate fractions, acid-treated oils, mildly solvent-refined oils, mildly treated hydrotreated oils, aromatic oils (including solvent extracts and high-boiling-point fractions of catalytically cracked oils), and some cutting oils caused skin tumors in mice. High-boiling-point fractions of cracked oils also caused skin tumors in rabbits and monkeys (IARC 1984, 1987).

Properties

Mineral oils include lubricant base oils and products derived from them. The physical properties of lubricant oils vary widely, but generally are defined by crude oil source, carbon number distribution, boiling range, and viscosity. Mineral oils, which are refined from petroleum crude oils, are complex mixtures of straight- and branched-chain paraffinic, naphthenic, and aromatic hydrocarbons with 15 or more carbons and boiling points in the range of 300°C to 600°C; boiling points of up to 815°C have been reported for heavier oils. The viscosity of lubricant oils is described as “light” or “heavy” depending upon whether the maximum viscosity at 37.8°C is less than or equal to 20.5 mm²/sec (centistokes). The density of mineral oils at 15°C ranges from 0.820 kg/L for light paraffinic base and process oils to just over 1.0 kg/L for high aromatic base and process oils. The complete description of a mineral oil must include the nature of the final treatment step, which determines whether the material is mildly or severely treated during the refining process. Medicinal white mineral oils, which are pharmaceutical- and food-grade materials, are highly refined and free of all aromatic and unsaturated compounds. As highly refined oils, these products are not covered under this listing (IARC 1984).

Mineral oils are insoluble in water and alcohol, but soluble in benzene, chloroform, ether, carbon disulfide, and petroleum ether. Paraffinic crude oils are characterized by high wax content, high natural viscosity index (the rate of change of viscosity over a given temperature range), and relatively low aromatic hydrocarbon content. Naphthenic crude oils are generally low in wax content and relatively high in cycloparaffins and aromatic hydrocarbons. All crude oils contain some polycyclic aromatic hydrocarbons, and the proportions and types of these compounds in finished base oils are determined primarily by the refining processes (IARC 1984). Mineral oils generally do not present a fire hazard and must be preheated before ignition will occur (HSDB 2009).

Use

Mineral oils are used primarily as lubricant base oils to produce further refined oil products, including engine oils, automotive and industrial gear oils, transmission fluids, hydraulic fluids, circulating and hydraulic oils, bearing oils, machine oils, machine-tool oils, compressor and refrigerator oils, steam-engine oils, textile machine oils, air-tool oils, metalworking oils (cutting oils, roll oils, can-forming oils, and drawing oils), rust-preventative oils, heat-treating oils, transformer oils, greases, medicinal and technical-grade white oils, and processing oils (product extenders, processing aids, carriers and diluents, water repellents, surface-active agents, batching oils, mold-release oils, and wash oils). These oils are used in manufacturing (78.5% of the oils produced), mining (5.0%), construction (1.8%), and miscellaneous industries (14.7%). About 57% of the lubricating oils produced are used by the automotive industry, and the remaining 43% by other industries. In the automotive industry, lubricating oils are used as multigrade engine oils (23% of the lubricating oils produced), monograde engine oils (22%), transmission and hydraulic fluids (8%), gear oils (2%), and aviation oils (1%). In other industries, lubricating oils are used as general industrial diesel engine oils (19%), process oils (13%), metalworking oils (4%), railroad diesel engine oils (3%), and marine diesel engine oils (2%) (IARC 1984).

Production

In 1981, about 19 billion pounds of mineral oil products were used in the United States (NPRA 1981), including 16.2 billion pounds of lubricating oils, 1.5 billion pounds of waxes, 814 million pounds of aromatic oils, and 462 million pounds of greases. In 2009, mineral oils were available from 28 U.S. suppliers (ChemSources 2009). In 1984, the United States imported 17,000 kg (37,000 lb) and exported 75,000 kg (165,000 lb) of mineral oil (type not specified) (HSDB 2009).

Exposure

The primary routes of potential human exposure to mineral oils are inhalation, ingestion, and dermal contact. The major hydrocarbon constituents of lubricant base oils and derived products occur naturally in crude petroleum. The general population potentially is exposed to unused and used mineral oils that occur naturally or are present as environmental contaminants. About 2 billion liters (528 million gallons) of used lubricating oils are released into the environment every year, including 750 million liters (198 million gallons) used as road oil or in asphalt (IARC 1984).

Occupational exposure to mineral oils may occur among workers employed in the manufacture of automobiles, airplanes and parts, steel products, screws, pipes, precision parts, and transformers, as well as workers employed in brass and aluminum production, engine repair, copper mining, and newspaper and commercial printing (IARC 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,009,473 workers, including 392,294 women, potentially were exposed to mineral oils (NIOSH 1990). The National Institute for Occupational Safety and Health reported the presence of mineral oils in the occupational environment of several plants in the 1970s. The concentration of cutting-oil mist was reported to be 0.37 to 0.55 mg/m³ for polishing of aircraft engine blades, 0.4 to 6.0 mg/m³ for machining of rough iron castings into automotive parts, 1.1 to 20 mg/m³ for manufacture of aircraft components, 0.3 to 1.3 mg/m³ for manufacture of automotive parts, from less than 0.03 to 0.8 mg/m³ for fabrication of precision metal parts, and from less than 0.035 to 3.1 mg/m³ for milling and machining operations. The concentration of transformer oil in air was re-

ported to be 0.1 to 1.4 mg/m³ for the manufacture and overhauling of large transformers (IARC 1984).

Regulations

Consumer Product Safety Commission (CPSC)

Products containing 10% or more of petroleum distillates require special labeling because of aspiration hazard.

Special packaging is required for certain household products containing 10% or more petroleum distillates and with a viscosity less than 100 Saybolt Universal seconds.

Environmental Protection Agency (EPA)

Clean Water Act

Procedures, methods, equipment, and other requirements have been established to prevent the discharge of all types of oils (including mineral oil) from all types of non-transportation-related facilities.

Products of mineral oil origin at levels that will cause interference are banned from discharge to publicly owned treatment works.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerance for residues of mineral oil on corn, grain, and sorghum = 200 ppm.

Food and Drug Administration (FDA)

Some over-the-counter drugs and products containing mineral oil must contain a warning label.

Restrictions on the use of mineral oil in food preparation and in packaging materials are prescribed in 21 CFR 172, 173, and 175-179.

When used as a lubricant with incidental food contact, mineral oil levels shall not exceed 10 ppm.

Drugs for internal use containing mineral oil must have a warning label.

Limitations on the use of mineral oil in drugs for use in animal feed are prescribed in 21 CFR 558.

Limits on the use of mineral oil as an additive in feed and drinking water of animals are prescribed in 21 CFR 573.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 5 mg/m³ for mineral-oil mist.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 5 mg/m³ for mineral-oil mist.

Threshold limit value – short term exposure limit (TLV-STEL) = 10 mg/m³ for mineral-oil mist.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 5 mg/m³ for mineral-oil mist.

Short-term exposure limit (STEL) = 10 mg/m³ for mineral-oil mist.

Immediately dangerous to life and health (IDLH) limit = 2,500 mg/m³ for mineral-oil mist.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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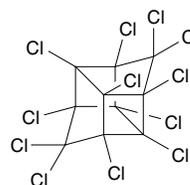
Mirex

CAS No. 2385-85-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-1,3,4-metheno-1H-cyclobuta[cd]pentalene



Carcinogenicity

Mirex is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Mirex caused tumors in mice and rats by two different routes of exposure. It caused benign or malignant liver tumors after (1) administration to infant mice of both sexes by stomach tube for three weeks, followed by dietary exposure, (2) dietary administration to rats of both sexes, and (3) a single subcutaneous injection in male mice. An excess of lymphoma (reticulum-cell sarcoma) observed in male mice exposed by subcutaneous injection also may have been related to mirex exposure (IARC 1974, 1979).

Since mirex was listed in the *Second Annual Report on Carcinogens*, additional studies in rats have been identified. Dietary administration of mirex caused benign liver tumors (adenoma) in both sexes, benign tumors of the adrenal glands (pheochromocytoma) and kidney (transitional-cell papilloma) in males, and mononuclear-cell leukemia in females (NTP 1990).

Cancer Studies in Humans

The data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to mirex.

Properties

Mirex is a chlorinated insecticide that is an odorless snow-white crystal at room temperature (HSDB 2009). Mirex is practically insoluble in water, but is soluble in dioxane, xylene, benzene, carbon tetrachloride, and methyl ethyl ketone. It is very stable at normal temperatures and pressures (Akron 2009). Physical and chemical properties of mirex are listed in the following table.

Property	Information
Molecular weight	545.6 ^a
Melting point	485°C ^a
Log <i>K</i> _{ow}	5.28 ^a
Water solubility	0.085 mg/L at 25°C ^b
Vapor pressure	8 × 10 ⁻⁷ mm Hg at 25°C ^b
Vapor density relative to air	18.8 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Mirex was used in the United States from 1959 until 1972 as a fire-retardant additive and as an insecticide to control fire ants in southeastern states; the latter use continued until 1978 (IARC 1979, ATSDR

1995). From 1962 to 1976, 132 million acres in nine states were treated for fire-ant control with about 500,000 lb of mirex bait, primarily by aerial application. Mirex was also used to control other species of ants, yellow jackets, and mealy bugs in pineapples (IARC 1979). The U.S. Environmental Protection Agency canceled all registered uses of mirex in December 1977; however, selected applications were allowed until existing stocks were exhausted in June 1978.

Production

Mirex was first synthesized in the mid 1940s, but it did not become commercially available in the United States until 1958 (IARC 1979). Technical-grade mirex was produced commercially by one company in the United States until 1967. The insecticidal baits were produced until 1975, when all registrations and the rights to produce and sell baits containing mirex were transferred to the Mississippi Department of Agriculture until the supply of mirex was exhausted. One company produced an estimated 3.3 million pounds of mirex between 1959 and 1975 and purchased an additional 1.5 million pounds from another company (ATSDR 1995). Peak production occurred from 1963 to 1968. U.S. production was 41,500 lb in 1972 and less than 1,000 lb in 1975 (HSDB 2009). Mirex is available in small quantities for laboratory use from seven U.S. suppliers and four other suppliers worldwide (ChemSources 2009). Before cancellation of its registrations for technical products, mirex was imported from Brazil; however, no data on U.S. import volumes were found (ATSDR 1995). Over 90% of the mirex produced in the United States between 1950 and 1975 was exported.

Exposure

Although mirex is no longer produced or used in the United States, it is very persistent in the environment and is highly resistant to degradation. Because mirex remains in the environment for a long time, the general population may continue to be exposed at low concentrations (ATSDR 1995). Populations with the greatest potential for exposure include those who eat fish from contaminated water bodies, reside near a former mirex manufacturing or waste-disposal site, or live in areas where mirex was extensively used to control fire ants.

Mirex has a half-life of up to 10 years in the environment. It is very soluble in fat and bioaccumulates in animals. Mirex has been found in Antarctic species, indicating that it is transported over long distances (Bustnes *et al.* 2006). It has been measured in top avian predators at both poles; however, concentrations were much higher in the Antarctic species. The one U.S. plant that manufactured mirex was located on the Niagara River upstream from Lake Ontario. It was estimated that almost 6,000 lb of mirex entered Lake Ontario from that facility. From 1977 to 1999, concentrations of mirex in salmon fillets collected from Lake Ontario declined by more than tenfold, to less than 0.1 mg/kg; the decline was attributed to clean-up of the groundwater discharge from the former manufacturing site, resulting in less mirex available in Lake Ontario for biomagnification in the food chain (Makarewicz *et al.* 2003). In another study, mirex was found at concentrations of up to 360 ng/g in lake trout taken near the former manufacturing site; in lake trout in the other Great Lakes, it was found at much lower concentrations or was below the limit of detection (2 ng/g) (Hickey *et al.* 2006). In Arctic Greenland populations, the daily intake of mirex increased from 0.002 µg/kg of body weight in 1976 to 0.0044 µg/kg in 2004, even though the consumption of traditional foods declined (Deutch *et al.* 2004).

Mirex has been found in the blood of numerous human populations, especially in indigenous people of northern regions (Van Oostdam *et al.* 2004). A survey of organochlorine pesticides in maternal blood found mirex at concentrations up to 12 µg/kg of serum lipids

in Arctic populations in Greenland, Canada, Alaska, Norway, Sweden, Iceland, Finland, and Russia. The blood levels of mirex in Greenland arctic populations ranged from 34.1 to 88.1 µg/kg of lipid and correlated with Inuit consumption of seal and fish (Deutch *et al.* 2004). In Arctic Canada, mirex was detected in 84% of Inuit maternal blood samples at a mean concentration of 0.07 µg/L, but in less than 45% of samples from other ethnic groups, at a median concentration of only 0.02 µg/L. However, it was detected in only 8.5% of the corresponding cord blood plasma samples from all ethnic groups, at a mean concentration of 0.01 µg/L (Butler Walker *et al.* 2003).

Mirex was found in 46% of the blood samples collected from Akwesasne Mohawk youth living along the St. Lawrence River in New York and Quebec, at a mean concentration of 0.036 ppb. Levels were somewhat higher in youths who had been breastfed as infants, but the difference was not statistically significant (Schell *et al.* 2003). In Montreal, mirex was found in the blood of ethnic Bangladeshi and Vietnamese fishermen and in majority-community sport fishers; concentrations were highest among the majority sport fishers, because they caught and ate larger fish (Kosatsky *et al.* 1999). In a study of male sport fishers in New York State, their mean blood mirex concentration was 18.4 ng/g of lipid, significantly higher than in non-consumers of sport fish (Bloom *et al.* 2005). A study in the Great Lakes also found higher blood concentrations of mirex among men and women who consumed fish than in non-consumers (Kearney *et al.* 1999). Mirex was found in 86% of the blood samples collected from pregnant women in an agricultural community in California, at a median concentration of 0.29 ng/g of lipid (Fenster *et al.* 2006). A study in southern Spain measured organochlorine pesticides in 150 placentas and detected mirex in 40% of the samples, at a mean concentration of 0.38 ng/g of placenta (Lopez-Espinosa *et al.* 2006).

Mirex was found in all adipose-tissue samples collected at autopsy from Greenlanders; the highest mean concentration, 126 µg/kg of lipid, was found in omental fat. This was lower than found in a previous study of Greenlanders, but much higher than in studies conducted in other locations (Deutch *et al.* 2006). Breast-milk concentrations of mirex also were elevated in populations of women in New York State who had eaten contaminated local fish (Greizerstein *et al.* 1999, Fitzgerald *et al.* 2001).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 932 workers potentially were exposed to mirex (HSDB 2009). However, occupational exposure is now limited to workers employed at hazardous-waste sites or those involved in remediation of sites contaminated with mirex (ATSDR 1995).

Regulations

Department of Transportation (DOT)

Mirex is considered a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Federal Insecticide, Fungicide, and Rodenticide Act
Registrations for all uses have been canceled.

Food and Drug Administration (FDA)

Action level in the edible portion of fish = 0.1 ppm.

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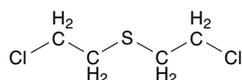
Mustard Gas

CAS No. 505-60-2

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as bis(2-chloroethyl) sulfide



Carcinogenicity

Mustard gas is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

In several epidemiological studies, exposure to mustard gas (through military use or occupationally) was associated with an increased risk

of lung or other respiratory-tract cancer. Among mustard-gas production workers, the risk of respiratory cancer was higher in individuals who had been exposed to mustard gas for longer periods (IARC 1975, 1987). Since mustard gas was listed in the *First Annual Report on Carcinogens* and subsequently reviewed by IARC (1987), it has been reported to be associated with cancer at several other tissue sites. A cohort study in England found significant excesses of laryngeal, pharyngeal, upper-respiratory-tract, and lung cancer in workers employed in the manufacture of mustard gas during World War II (Easton et al. 1988).

Cancer Studies in Experimental Animals

Mustard gas caused cancer in mice of both sexes. When administered by inhalation or intravenous injection, it caused lung tumors, and when administered by subcutaneous injection, it caused tumors at the injection site (fibrosarcoma or sarcoma) (IARC 1975, 1987).

Studies on Mechanisms of Carcinogenesis

Mustard gas caused genetic damage in all systems in which it was tested. It caused DNA damage in bacteria and gene mutations in fungi. In *Drosophila melanogaster*, it caused dominant lethal mutations, sex-linked recessive lethal mutations, aneuploidy, and heritable translocations. In cultured rodent cells, it caused mutations, chromosomal aberrations, and DNA damage. In mice exposed by intraperitoneal injection, mustard gas was shown to bind covalently to DNA, RNA, and protein (IARC 1987).

Properties

Mustard gas is a sulfur mustard alkylating agent that exists at room temperature as a colorless to yellow oily liquid with a sweet, agreeable odor (IARC 1975). It is insoluble in water, soluble in acetone, benzene, ethanol, ether, and other common organic solvents, miscible in petroleum ether, and highly soluble in lipids. It hydrolyzes readily in aqueous solution (Akron 2009). Physical and chemical properties of mustard gas are listed in the following table.

Property	Information
Molecular weight	159.1 ^a
Specific gravity	1.2741 at 20°C/4°C (liquid) 1.338 at 13°C (solid) ^a
Melting point	13°C to 14°C ^a
Boiling point	215°C to 217°C ^a
Log <i>K_{ow}</i>	2.41 ^b
Water solubility	0.000684 g/L at 25°C ^a
Vapor pressure	0.11 mm Hg at 25°C ^a
Vapor density relative to air	5.4 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Mustard gas is a vesicant (blister-inducing agent) first used in chemical warfare in World War I. It was also used in chemical warfare in Ethiopia in 1936 and in the Iran-Iraq war from 1984 to 1988. Small amounts are used in research as a model compound in biological studies of alkylating agents. Mustard gas was tested as an anticancer agent, but its clinical use was not successful because of its high toxicity (IARC 1975, ATSDR 2003).

Production

By the end of World War I, daily U.S. production of mustard gas had reached about 18,000 kg (40,000 lb). The United States continued to produce and stockpile mustard-gas chemical weapons until 1968, accumulating more than 34 million pounds (ATSDR 2003). The United States no longer produces, imports, or exports mustard gas

and signed the International Chemical Weapons Convention treaty in 1997, which mandated destruction of all chemical weapons by 2007 (CDC 2010). In 2009, mustard gas was available in research quantities from U.S. supplier (ChemSources 2009).

Exposure

The primary routes of potential human exposure to mustard gas are inhalation and dermal contact; however, the general population typically is not exposed to mustard gas. Aging stockpiles of mustard gas are stored at eight U.S. Army bases and are scheduled for destruction. Although the greatest risk of exposure to date has been among military personnel, there is some small risk of exposure for people living near military installations where mustard gas is stockpiled and destroyed or in the event of accidental releases or a chemical-warfare attack. People may also be exposed to residues of mustard gas disposed of in bulk quantities years or even decades ago if these disposal sites are disturbed (ATSDR 2003, HSDB 2009).

Bullman and Kang (1994) reviewed the effects of mustard gas and other hazards on U.S. military personnel. During World War I, as many as 28,000 of the American Expeditionary Forces were exposed to mustard gas, but seldom to lethal concentrations, because the gas was dispersed on the battlefield. Although mustard gas was not used in World War II, the United States produced and stockpiled it for possible use and conducted research to prepare for the threat of chemical-warfare attack. Top-secret experiments to test protective equipment, clothing, and antivesicant ointments, involving patch or drop tests, chamber tests, and field tests, were conducted with military volunteers. In the patch or drop tests, which assessed the strength of protective ointments, 15,000 to 60,000 soldiers and sailors were exposed to mustard gas. In chamber tests, protective masks and clothing were evaluated by exposure of volunteers to the chemical in a gas chamber for an hour or more every day or every other day until penetration was observed, evidenced by moderate to intense chemical burns on the skin. The same outcome was sought in field tests of the quality of masks, protective clothing, and ointments, which required soldiers to cross tropical or subtropical lands where the gas was dropped. In chamber and field tests, at least 4,000 servicemen were exposed to mustard gas.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Threshold planning quantity (TPQ) = 500 lb.

Reportable quantity (RQ) = 500 lb.

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

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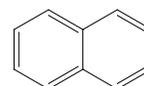
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Naphthalene

CAS No. 91-20-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Naphthalene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure of rats to naphthalene by inhalation caused nasal tumors, which are rare in this species. Two types of nasal tumor were observed: olfactory epithelial neuroblastoma of the nose, which is a highly malignant and extremely rare tumor of the lining of the nose, and respiratory epithelial adenoma, which also is rare (NTP 2000). At the time the National Toxicology Program study was published, neither type of tumor had been observed in the historical controls (299 males and females) in NTP two-year studies that used the same feed as the naphthalene bioassay. (As of 2010, no nasal tumors had been observed in 1,297 male or 1,247 female controls.) The incidence of neuroblastoma of the olfactory epithelium increased with increasing exposure level in both sexes and was significantly increased at the highest exposure level in females. Some of the neuroblastomas also invaded the brain. The incidence of respiratory epithelial adenoma was significantly increased in males, but not in females. In female B6C3F₁ mice, inhalation exposure to naphthalene caused lung tumors (NTP 1992). The International Agency for Research on Cancer (2002) concluded that there was sufficient evidence for the carcinogenicity of naphthalene in experimental animals.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to naphthalene. Two case-series studies of cancer in individuals exposed to naphthalene were identified; the first study reported cancer of the larynx and at other tissue sites among German workers occupationally exposed to naphthalene, and the second reported colorectal cancer among Africans who had used a naphthalene compound for medicinal purposes (Ajao *et al.* 1988, NTP 2002).

Studies on Mechanisms of Carcinogenesis

Naphthalene caused mutations in insects, but not in bacteria or cultured human lymphoblastoid cells (Sasaki *et al.* 1997, Grosovsky *et al.* 1999, NTP 2002). It caused other types of genetic damage in some but not all test systems. In newt larvae, naphthalene induced micronucleus formation. In cultured mammalian cells, it caused chromosomal aberrations, sister chromatid exchange, and formation of kinetochore-negative micronuclei, but did not cause DNA strand

breaks, formation of kinetochore-positive micronuclei, or cell transformation. Inhalation exposure of rats to naphthalene caused oxidative stress and DNA damage in liver and brain tissue (IARC 2002, NTP 2002).

When administered to experimental animals dermally, orally, or by inhalation, naphthalene is rapidly absorbed and metabolized (NTP 2000). Evidence suggesting that naphthalene is absorbed in humans comes from studies of workers in a coke plant, which found that concentrations of naphthalene metabolites in the urine were significantly correlated with concentrations of naphthalene in personal air samples (Bieniek 1994, 1997). The first step in the metabolism of naphthalene is formation of naphthalene-1,2-oxide (as two stereoisomers, 1*R*,2*S*-oxide and 1*S*,2*R*-oxide) through the action of cytochrome P450 enzymes in the presence of the coenzyme NADPH. These oxides are metabolized further by three pathways: (1) hydration by epoxide hydrolases into dihydrodiols, (2) conjugation by glutathione transferases, and (3) spontaneous rearrangement into 1-naphthol and 2-naphthol, which are converted to naphthoquinones (Chichester *et al.* 1994, Shultz *et al.* 1999). Naphthalene is excreted in the urine as the unchanged parent compound or as metabolites, including 1-naphthol, 2-naphthol, naphthoquinones, dihydroxynaphthalenes, and conjugated forms, including glutathione, cysteine, glucuronic acid, and sulfate conjugates (NTP 2002).

The mechanism by which naphthalene causes cancer is unknown. A strong correlation has been observed between the rates of formation of the stereoisomer (1*R*,2*S*)-naphthalene oxide in various tissues and the selective toxicity of naphthalene to these tissues, suggesting that this metabolite may play a role in naphthalene's toxicity to the lung and other tissues (Buckpitt and Franklin 1989). Oxidative damage and DNA breakage, observed in rat liver and brain tissue, may contribute to naphthalene's toxicity and carcinogenicity.

Properties

Naphthalene is a polycyclic aromatic hydrocarbon that exists at room temperature as a white crystalline solid with an aromatic odor. It is insoluble in water but soluble in methanol, ethanol, benzene, toluene, olive oil, turpentine, chloroform, carbon tetrachloride, ether, hydro-naphthalenes, fixed and volatile oils, and ethylene dichloride. It is stable in closed containers under normal temperatures and pressures (Akron 2009). Physical and chemical properties of naphthalene are listed in the following table.

Property	Information
Molecular weight	128.2
Density	1.162 g/cm ³ at 20°C
Melting point	80.2°C
Boiling point	217.9°C
Log <i>K</i> _{ow}	3.3
Water solubility	0.031 g/L at 25°C
Vapor pressure	0.085 mm Hg at 25°C
Vapor density relative to air	4.42

Source: HSDB 2009.

Use

The principal use of naphthalene in the United States is as an intermediate in the production of phthalic anhydride, which in turn is an intermediate in the production of phthalate plasticizers, pharmaceuticals, insect repellents, and other materials. Naphthalene has also been used as an intermediate in the production of 1-naphthyl-*N*-methylcarbamate insecticides, β-naphthol, synthetic leather-tanning chemicals, surfactants (e.g., naphthalene sulfonates), moth repellents, and toilet-bowl deodorizers (ATSDR 2005, HSDB 2009). In 1999, 59% of naphthalene was used for production of phthalic an-

hydride, 21% for production of surfactant and dispersant chemicals, 11% for production of insecticides, and 9% in moth repellents and for other purposes (CMR 1999). The Naphthalene Panel of the American Chemistry Council reported in 2002 that naphthalene was no longer used directly in tanneries, in the textile industry, or in the production of toilet-bowl deodorizers and that β-naphthol was not manufactured in the United States (ACC 2002).

Production

Naphthalene is produced from either coal tar (which contains approximately 10% naphthalene), by condensation and separation of coal tar from coke-oven gases, or from petroleum, by dealkylation of methyl-naphthalenes. In the United States, most naphthalene was produced from petroleum through the 1980s. U.S. production of naphthalene peaked in 1968, at 900 million pounds, decreasing to 222 million pounds by 1994 (ATSDR 2005). In 2000, production was 235 million pounds, of which over 90% (219 million pounds) was from coal tar (CEH 2000). In 2002, estimated U.S. production capacity was 215 million pounds (ATSDR 2005). In 2009, two U.S. producers of naphthalene were identified (SRI 2009).

From 1989 to 1998, U.S. demand for naphthalene grew 0.5% per year. Demand was 246 million pounds in 1998 and 248 million pounds in 1999. Demand for naphthalene sulfonates, used primarily as superplasticizer additives to increase the flowability of concrete, grew steadily in the late 1990s (CMR 1999). In 2000, estimated consumption of naphthalene was 241 million pounds (ATSDR 2005). In 2009, naphthalene was available from 28 U.S. suppliers (ChemSources 2009). Between 1989 and 2003, U.S. imports of naphthalene ranged from a high of 18.5 million kilograms (40.9 million pounds) in 1989 to a low of 1.1 million kilograms (2.5 million pounds) in 1999. In 2008, imports totaled 8.1 million kilograms (17.9 million pounds). Between 1989 and 2008, U.S. exports of naphthalene ranged from a low of 2.5 million liters (660,000 gallons) in 1993 to a high of 64.9 million liters (17.1 million gallons) in 1998; in 2009, exports were 4.8 million liters (1.3 million gallons) (USITC 2009).

Exposure

The general population potentially is exposed to naphthalene through inhalation of ambient and indoor air. Accidental ingestion of household products containing naphthalene, mainly by children, has been reported. Dermal exposure to naphthalene may occur through handling or wearing of clothing stored with moth repellents containing naphthalene. The average daily intake of naphthalene from ambient air was estimated at 19 μg, based on an average naphthalene concentration of 0.95 μg/m³ in urban and suburban air and an inhalation rate of 20 m³/day (ATSDR 2005). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of naphthalene have decreased annually since 1998, when almost 6 million pounds was released. In 2007, 983 facilities released over 2.7 million pounds of naphthalene, of which more than half was released to air (TRI 2009).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 112,700 workers potentially were exposed to naphthalene (NIOSH 1990). Workers identified by EPA as potentially exposed to naphthalene include beta-naphthol makers, celluloid makers, coal-tar workers, dye-chemical makers, fungicide makers, hydronaphthalene makers, moth-repellent workers, phthalic anhydride makers, smokeless-powder makers, tannery workers, textile-chemical workers, and aluminum reduction plant workers (EPA 1980). No more recent occupational exposure surveys were found. However, industry estimates in 2002 indicated that about 1,000 workers were employed by the largest U.S. tar-distillation and wood-preservation

company and that fewer than 50 workers in the moth-repellent industry potentially were exposed to naphthalene (ACC 2002). These estimates did not include workers potentially exposed to naphthalene in production of phthalic anhydride and other uses. Workplace air concentrations of naphthalene have been measured in many studies and vary by industry. In the vulcanization step of tire manufacturing, naphthalene was measured at concentrations of up to 1.09 mg/m³, resulting in an estimated daily intake of 0.0029 mg/kg of body weight (Durmusoglu 2007). A survey by the National Institute for Occupational Safety and Health in 1980 reported air concentrations of naphthalene as high as 10.2 µg/m³ in an area sample and 19.3 µg/m³ in a personal sample (ATSDR 2005).

Regulations

Department of Transportation (DOT)

Naphthalene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a substance for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of naphthalene = U165, F024, F025, F034, K001, K035, K087, K145.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 10 ppm (50 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm (50 mg/m³).

Threshold limit value – short-term exposure limit (TLV-STEL) = 15 ppm (75 mg/m³).

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 10 ppm (50 mg/m³).

Short-term exposure limit (STEL) = 15 ppm (75 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 250 ppm (1,250 mg/m³).

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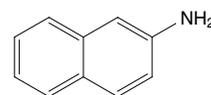
2-Naphthylamine

CAS No. 91-59-8

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as β-naphthylamine



Carcinogenicity

2-Naphthylamine is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or present as an impurity in other compounds, causes cancer of the urinary bladder. Studies of dye-stuff workers and of chemical workers exposed mainly to 2-naphthylamine found increased risks of urinary-bladder cancer that could not be explained by workers' smoking habits. At one dyestuff plant, the cancer risk increased with increasing exposure to 2-naphthylamine. In addition, many case reports have linked 2-naphthylamine exposure with urinary-bladder cancer in workers who manufactured or used 2-naphthylamine. The International Agency for Research on Cancer concluded that there was sufficient evidence for the carcinogenicity of 2-naphthylamine in humans (IARC 1974, 1987).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of 2-naphthylamine from studies in experimental animals. Oral exposure to 2-naphthylamine caused urinary-bladder cancer (carcinoma) in hamsters, dogs, and rhesus monkeys and benign liver tumors (hepatocellular adenoma) in mice (IARC 1974). Since 2-naphthylamine was listed in the *First Annual Report on Carcinogens*, additional studies in rodents have been identified. Oral administration of 2-naphthylamine to rats caused a low incidence of urinary-bladder cancer (carcinoma), and administration to mice by intraperitoneal injection caused benign lung tumors (adenoma) (IARC 1987).

Studies on Mechanisms of Carcinogenesis

2-Naphthylamine caused genetic damage in various test systems, including mutations in bacteria, yeast, insects, plants, cultured human and other mammalian cells, and experimental animals exposed *in vivo*. Other types of genetic damage observed in some of these systems included DNA strand breaks, chromosomal aberrations, micronucleus formation, aneuploidy, sister chromatid exchange, and cell transformation (IARC 1987, Gene-Tox 1998).

The mechanism by which 2-naphthylamine causes cancer is thought to require its metabolism to a reactive form. When arylamines, such as 2-naphthylamine, are metabolized, they are either activated via N-hydroxylation (by cytochrome P450 liver enzymes) or detoxified via pathways such as N-acetylation. The N-hydroxylamine metabolites can form adducts with blood-serum proteins (such as hemoglobin), which circulate freely, or they can undergo further metabolism (conjugation) to form reactive compounds that can be transported to the bladder and can bind to DNA (Yu *et al.* 2002). 2-Naphthylamine DNA adducts have been found in bladder and liver cells from exposed dogs (IARC 1987).

Properties

2-Naphthylamine is an aromatic amine (arylamine) that exists at room temperature as colorless crystals with a faint aromatic odor. It is soluble in hot water, alcohol, ether, and many organic solvents. 2-Naphthylamine oxidizes in the presence of air, and the vapors can be explosive (IARC 1974, Akron 2009). Physical and chemical properties of 2-naphthylamine are listed in the following table.

Property	Information
Molecular weight	143.2
Specific gravity	1.061 at 98°C/4°C
Melting point	111°C to 113°C
Boiling point	306°C
Log K_{ow}	2.28
Water solubility	0.00640 g/L at 18°C
Vapor pressure	2.56×10^{-4} mm Hg at 25°C
Vapor density relative to air	4.95
Dissociation constant (pK_a)	4.16

Source: HSDB 2009.

Use

2-Naphthylamine now is used only in laboratory research. It formerly was used as an intermediate in the manufacture of dyes, as an antioxidant in the rubber industry, and to produce 2-chloronaphthylamine (IARC 1974, HSDB 2009).

Production

2-Naphthylamine was commercially produced in the United States from at least the early 1920s to the early 1970s. In 1955 (the last year for which production data were found), 581,000 kg (1.3 million pounds) was produced by four manufacturers (IARC 1974). Since

its commercial manufacture and use were banned in the early 1970s, 2-naphthylamine has been available only in small quantities for laboratory research. In 2009, it was available from 10 U.S. suppliers (ChemSources 2009). 2-Naphthylamine has not been imported in significant amounts since 1967, when U.S. imports totaled 17,400 kg (38,400 lb) (IARC 1974).

Exposure

Because commercial production and use of 2-naphthylamine are banned, the potential for exposure is low. The general population may be exposed through inhalation of emissions from sources where nitrogen-containing organic matter is burned, such as coal furnaces and cigarettes (HSDB 2009). The U.S. Environmental Protection Agency's Toxics Release Inventory listed one industrial facility reporting releases of 2-naphthylamine for 1998 through 2001; none was released in 1998, and releases were 8 lb in 1999, 15 lb in 2000, and 265 lb in 2001. No records of earlier releases were found (TRI 2009). Mainstream cigarette smoke from eight different U.S. conventional market cigarettes contained 2-naphthylamine at concentrations of 1.5 to 14.1 ng per cigarette (Stabbert *et al.* 2003); other investigators reported levels as high as 35 ng per cigarette (Hoffman *et al.* 1997). For sidestream smoke, a concentration of 67 ng per cigarette was reported (Patrianakos and Hoffmann 1979). 2-Naphthylamine also occurs as an impurity (0.5% or less) in commercially produced 1-naphthylamine.

At greatest risk of occupational exposure to 2-naphthylamine are laboratory technicians and scientists who use it in research. Before U.S. commercial production of 2-naphthylamine and its use in the dye and rubber industries were banned, workers in these industries potentially were exposed. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 420 workers potentially were exposed to 2-naphthylamine (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 275 workers, including 265 women, potentially were exposed (NIOSH 1990).

Regulations

Department of Transportation (DOT)

2-Naphthylamine is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 2-naphthylamine = U168.
Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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Nickel Compounds and Metallic Nickel

Introduction

Nickel compounds and metallic nickel have many industrial and commercial applications, including use in stainless steel and other nickel alloys, catalysts, batteries, pigments, and ceramics. Nickel and Certain Nickel Compounds were listed in the *First Annual Report on Carcinogens* (1980) as *reasonably anticipated to be human carcinogens*. Nickel compounds as a class were first listed as *known to be human carcinogens* in the *Tenth Report on Carcinogens* (2002); this listing supersedes the listing of "certain nickel compounds" and applies to all members of the class. Metallic nickel was reevaluated in 2000 and remains listed as *reasonably anticipated to be a human carcinogen*. Nickel alloys were reviewed in 2000 but were not recommended for listing in the Report on Carcinogens (see Appendix C).

The profiles for nickel compounds and metallic nickel follow this introduction. The evidence for carcinogenicity from cancer studies in experimental animals and humans is discussed separately for nickel compounds and metallic nickel. However, most of the information on mechanisms of carcinogenesis, properties, use, production, exposure, and regulations is common to both nickel compounds and metallic nickel and therefore is combined into one section following the discussions of cancer studies.

Nickel Compounds

No separate CAS No. assigned for lead compounds as a class

Known to be human carcinogens

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Nickel compounds are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic studies. The combined results of epidemiological studies, mechanistic studies, and cancer studies in rodents support the concept that nickel compounds generate nickel

ions in target cells at sites critical for carcinogenesis, thus allowing consideration and evaluation of these compounds as a single group.

Cancer Studies in Humans

Several epidemiological cohort studies of workers exposed to various nickel compounds showed an elevated risk of death from lung cancer and nasal cancer. Although the precise nickel compound responsible for the carcinogenic effects in humans is not always clear, studies indicate that nickel sulfate and the combinations of nickel sulfides and oxides encountered in the nickel-refining industry cause cancer in humans. The International Agency for Research on Cancer concluded that there was sufficient evidence of the carcinogenicity of nickel compounds encountered in the nickel-refining industry in humans (IARC 1990). In an additional study, nickel-refinery workers exposed primarily to soluble nickel compounds had a significant excess risk of lung cancer, and smoking and nickel exposure had a synergistic effect on cancer risk (Anderson *et al.* 1996). These workers also had an excess risk of nasal cancer.

Cancer Studies in Experimental Animals

In rats and in some studies with mice, inhalation or intratracheal instillation of nickel subsulfide or nickel oxide led to dose-related induction of benign and malignant lung tumors, including carcinoma (IARC 1990, NTP 1996a,b). Inhalation of nickel compounds also caused tumors at tissue sites other than the lung; in particular, benign or malignant adrenal-gland tumors (pheochromocytoma) were observed in rats (NTP 1996a,b). Injection of rodents with various nickel compounds was repeatedly shown to cause dose-dependent increases in tumors in several species and at several different sites. Subcutaneous, intramuscular, intraperitoneal, subperiosteal, intrafemoral, intrapleural, intracerebral, intrarenal, intratesticular, and intraocular injections of nickel compounds all caused cancer (usually sarcoma) at the injection site. Injection of nickel also produced distant tumors of the liver in some strains of mice. IARC concluded that there was sufficient evidence of the carcinogenicity of several nickel compounds (monoxides, hydroxides, and crystalline sulfides) in experimental animals (IARC 1990).

Soluble nickel acetate is a complete transplacental carcinogen in rats. Brief exposure of pregnant rats to nickel acetate by intraperitoneal injection during pregnancy caused pituitary cancer in the offspring. Transplacental exposure to nickel acetate followed by exposure of the offspring to barbital (a known tumor promoter) caused kidney tumors (renal cortical and pelvic tumors) (Diwan *et al.* 1992). In adult rats, injection of soluble nickel salts followed by barbital exposure caused kidney cancer (renal cortical adenocarcinoma) that frequently metastasized to the lung, liver, and spleen (Kasprzak *et al.* 1990).

Metallic Nickel

CAS No. 7440-02-0

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as Ni

Carcinogenicity

Metallic nickel is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Metallic nickel caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. In both rats and hamsters, metallic nickel powder caused tumors when administered by intratracheal instillation or by subcutaneous, intramuscular, or intraperitoneal injection. Intratracheal instillation of metallic nickel powder primarily caused adenocarcinoma, whereas injection most frequently caused sarcoma, demonstrating that metallic nickel can induce both epithelial and connective-tissue tumors (IARC 1973, 1976, 1990).

Cancer Studies in Humans

The available epidemiological studies of workers exposed to metallic nickel are limited by inadequate exposure information, low exposure levels, short follow-up periods, and small numbers of cases.

Nickel Compounds and Metallic Nickel

Studies on Mechanisms of Carcinogenesis

The available evidence suggests that metallic nickel has carcinogenic properties because it can slowly dissolve in the body and release ionic nickel, an active genotoxic and carcinogenic form of nickel. There is no evidence to suggest that the mechanisms by which nickel causes tumors in experimental animals would not also operate in humans.

Many studies in cultured rodent and human cells have shown that a variety of nickel compounds, including both soluble and insoluble forms of nickel, caused genetic damage, including DNA strand breaks, mutations, chromosomal damage, cell transformation, and disrupted DNA repair. Chromosomal aberrations have been observed in humans occupationally exposed to nickel. Nickel can bind ionically to cellular components, including DNA. The reduction-oxidation activity of the nickel ion may produce reactive oxygen species that attack DNA, and exposure to nickel ion *in vitro* or *in vivo* can result in production of 8-hydroxy-2'-deoxyguanosine in target tissues for cancer caused by nickel (IARC 1990, Kasprzak *et al.* 1990).

The carcinogenic potency of various nickel compounds varies widely, based on solubility properties and speciation. Studies indicate that soluble nickel salts can be complete carcinogens (Diwan *et al.* 1992) or initiators of carcinogenesis (Kasprzak *et al.* 1990) at tissue sites distant from the site of administration, which confirms that ionic nickel is the carcinogenic species. Differences in the potency of nickel compounds may relate to the specific properties of the compounds that affect the availability of ionic nickel at target sites. The listings of nickel compounds and metallic nickel are based on a large body of scientific evidence supporting the concept that nickel ion is carcinogenic. The hazard associated with a particular nickel compound is related largely to the compound's propensity to release ionic nickel in the body. The evidence suggests that the relatively insoluble metallic nickel is less likely to present a carcinogenic hazard than are the nickel compounds that tend to release proportionately more nickel ion. This view agrees with that expressed by IARC (1990), which based its evaluation of the carcinogenicity of nickel compounds as a group on the combined results of human epidemiological studies, cancer studies in experimental animals, and other data supporting the "underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells." The IARC review noted that the carcinogenicity of nickel compounds depends not solely on their capacity to release ionic nickel, but also on factors that promote localization of high concentrations of nickel ions at critical tissue sites. This conclusion is consistent with evidence from studies in experimental animals indicating that nickel compounds of moderate solubility can,

under certain exposure conditions, be more carcinogenic than more soluble compounds. Therefore, it is difficult to predict with any certainty the relative carcinogenic hazard posed by a particular nickel compound without a full understanding of its ability to release ionic nickel under specific exposure conditions.

Properties

Metallic nickel is a group 10 metallic element. It is a lustrous, silvery, hard ferromagnetic metal or a gray powder. It has a vapor pressure of 1 mm Hg at 1,810°C. Metallic nickel is insoluble in water and ammonia, slightly soluble in hydrochloric acid and sulfuric acid, and soluble in dilute nitric acid. It is resistant to attack by air and water at standard temperatures. However, powdered nickel is reactive in air and may ignite spontaneously (IARC 1990, ATSDR 1997, HSDB 2009).

Nickel oxides and hydroxides are practically insoluble in water and soluble in acids and ammonium hydroxide. Nickel monoxide (also known as nickel oxide) is a green to black powder that becomes yellow when heated. The temperature at which the crystal is formed determines the color of the crystal. It is soluble in acids and ammonium hydroxide. Nickel monoxide reacts with acids to form nickel salts and soaps, and mixtures of nickel monoxide and barium oxide react violently with iodine and hydrogen sulfide in air. Nickel hydroxide occurs either as green crystals or as a black powder. It does not burn, but it may produce toxic gases when heated to decomposition. It is available at 97% purity (IARC 1990, HSDB 2009).

Nickel sulfides are insoluble in water, and some occur in more than one form. Nickel subsulfide (α form) occurs as lustrous pale-yellowish or bronze crystals that are soluble in nitric acid. Nickel sulfide occurs in three forms (α , β , and amorphous) as dark-green to black crystals or powder. Nickel disulfide occurs as black crystals or powder and decomposes at temperatures above 400°C (IARC 1990).

Nickel salts are green to yellow crystals that generally are soluble in water and decompose when heated. Nickel acetate occurs as a dull-green powder that effloresces somewhat in air. It is available as the tetrahydrate at greater than 97% purity. Nickel chloride occurs as yellow (anhydrous) or green (hexahydrate) deliquescent crystals. It is soluble in ethanol and ammonium hydroxide and insoluble in ammonia. The hexahydrate form is available as a laboratory reagent at greater than 99% purity or as industrial products containing approximately 24.7% nickel. Nickel sulfate occurs as yellow, green, or blue crystals and is available in anhydrous, hexahydrate, or heptahydrate forms. The hexahydrate melts at 53.3°C and the heptahydrate at 99°C; both forms are available at greater than 99% purity. Nickel carbonate occurs as light-green rhombic crystals. It is practically insoluble in water but soluble in dilute acids and ammonia. Laboratory reagent grades contain 45% or 47.5% nickel, and industrial grades contain approximately 45% nickel (IARC 1990, HSDB 2009).

Nickel carbonyl occurs as a colorless, volatile, highly flammable liquid with a musty odor. It is practically insoluble in water but soluble in alcohol, benzene, chloroform, acetone, and carbon tetrachloride, and insoluble in dilute acids and dilute alkalis. It is available in a technical grade at greater than 99% purity. Nickel carbonyl decays spontaneously in air and may decompose violently when exposed to heat or flame in the presence of air or oxygen. When heated or on contact with acid or acid fumes, it emits toxic carbon monoxide fumes (HSDB 2009). Nickelocene occurs as dark-green crystals. It is insoluble in water but soluble in common organic solvents. It is highly reactive and decomposes in air, acetone, alcohol, and ether. It is available in solid form at greater than 90% purity or as an 8% to 10% solution in toluene (IARC 1990).

Physical and chemical properties of metallic nickel and selected nickel compounds are listed in the table below, along with their chemical formulas.

Use

Because of its unique properties, nickel has many uses in industry. The majority (about 80%) of all nickel is used in alloys, because it imparts such properties as corrosion resistance, heat resistance, hardness, and strength (ATSDR 1997). The main uses of nickel are in the production of stainless steel, copper-nickel alloys, and other corrosion-resistant alloys. Pure nickel metal is used in electroplating, as a chemical catalyst, and in the manufacture of alkaline batteries, coins, welding products, magnets, electrical contacts and electrodes, spark plugs, machinery parts, and surgical and dental prostheses (IARC 1990, HSDB 2009). In 2009, 45% of the nickel used in the United States was used in stainless and alloy steel production, 39% in nonferrous alloys and superalloys, 11% in electroplating, and 5% in other uses. The end uses in 2009 were 32% in transportation, 14% in the chemical industry, 10% in electrical equipment, 8% in construction, 8% in fabricated metal products, 8% in the petroleum industry, 6% in household appliances, 6% in machinery, and 8% for other uses (Kuck 2010).

Nickel oxide sinters (a coarse form of nickel monoxide) are used in steel and alloy manufacturing. Green nickel monoxide is used in electronics, in fuel-cell electrodes, as a colorant in ceramics and glass, and to make nickel catalysts. Black nickel monoxide is used in the ceramics industry, to manufacture nickel catalysts, and to manufacture nickel salts. Nickel hydroxide is used in nickel-cadmium batteries and as a catalyst intermediate. Nickel sulfides are used as catalysts in the petrochemical industry when high concentrations of sulfur are present in the distillates and as intermediates in hydrometallurgical processing of silicate-oxide nickel ores (IARC 1990). Nickel subsulfide is used in lithium batteries (HSDB 2009).

Nickel salts are widely used in industry. Nickel acetate is used as a catalyst intermediate, as a dye fixative in the textile industry, in electroplating, and as a sealer for anodized aluminum. Nickel chloride is used in nickel catalysts, to absorb ammonia in industrial gas masks, and in electroplating. Nickel sulfates are used in electroplating and electrodeless nickel plating, as chemical intermediates to produce other nickel compounds, and in nickel flashings on steel to prepare it to be porcelain-enameled. Nickel carbonate is used to prepare nickel monoxide, nickel powder, nickel catalysts, colored glass, and certain nickel pigments. It also is used in electroplating and as a catalyst to remove organic contaminants from water (IARC 1990, HSDB 2009).

Nickel carbonyl is used in the production of high-purity nickel powder by the Mond process and for continuous nickel coatings on steel and other metals. It also has many small-scale applications, such as vapor plating of nickel and deposition of nickel in semiconductor manufacturing. Nickelocene is used as a catalyst and complexing agent (IARC 1990).

Production

Nickel is refined from either sulfide or silicate-oxide ores, which generally contain no more than 3% nickel. Magmatic sulfide ores are mined underground or by open-pit methods. Pentlandite ($[\text{NiFe}]_9\text{S}_8$) is the principal sulfide ore; the largest known deposit is in Ontario, Canada, and substantial deposits are found in Minnesota, South Africa, Russia, Finland, and western Australia. Silicate-oxide ores, or garnierites, originate in (current or former) humid tropical regions and are surface mined by open-pit methods (IARC 1990, ATSDR 1997). Primary nickel production from mines in the United States was steady from the late 1950s to 1980, ranging from 10,000 to 14,000 metric tons (22 million to 31 million pounds) per year (USGS 2010). After 1980, primary production of nickel in the United States started declining, and no primary production has occurred since 1998, when 4,290 metric tons (9.5 million pounds) was produced.

Recycled scrap metal accounts for a large part of the nickel supply; in addition, relatively small quantities of nickel are recovered as a by-product at copper and precious-metal refineries or from reclamation of spent catalysts (Kuck 2009). Production from these secondary sources increased steadily from 21,000 metric tons (46 million pounds) in 1970 to a high of 106,000 metric tons (234 million pounds) in 2006, then declined to 63,500 metric tons (140 million pounds) in 2009.

From 1980 to 2008, U.S. consumption of nickel ranged from 163,000 to 250,000 metric tons (359 to 551 million pounds); consumption was highest in 2006 (USGS 2010). In 2009, consumption was 152,000 metric tons (335 million pounds), the lowest level since 1972 (Kuck 2010, USGS 2010). The demand for nickel is expected to grow because of increased demand for nickel-based batteries and nickel-bearing superalloys used in aircraft engines (Kuck 2009), with the United States being dependent on foreign sources for most nickel supplies.

From 1980 to 2008, U.S. imports of nickel remained fairly steady, ranging from 117,000 to 190,000 metric tons (258 million to 419 million pounds); 149,000 metric tons (329 million pounds) was imported in 2008. In 2009, imports fell to 114,800 metric tons (253 million pounds). U.S. exports of nickel ranged from 17,700 to 67,300 metric tons (39 to 148 million pounds) between 1980 and 2006, increasing to 116,000 metric tons (256 million pounds) in 2007, and were 99,680 metric tons (220 million pounds) in 2009 (Kuck 2010, USGS 2010).

Exposure

Environmental exposure to nickel occurs through inhalation, ingestion, and dermal contact. The general population is exposed to low levels of nickel because it is widely present in air, water, food, and consumer products. The general population takes in most nickel through food; the average daily intake from food in the United States is estimated at 150 to 168 μg . Typical daily intake from drinking water is 2 μg and from air is 0.1 to 1 μg . The general population is also ex-

Substance	Formula	Atomic or molec. wt.	Specific gravity	Melting point	Boiling point
Metallic nickel	Ni	58.7	8.91	1,455°C	2,730°C
Nickel monoxide	NiO	74.7	6.72	1,955°C	NR
Nickel hydroxide	Ni(OH) ₂	92.7	4.1	230°C (dec)	N/A
Nickel acetate	Ni(C ₂ H ₃ O ₂) ₂	176.8	1.80	NR	16.6°C
Nickel chloride	NiCl ₂	129.6	3.51	1,001°C	973°C (sub)
Nickel sulfate	NiSO ₄	154.8	4.01	848°C (dec)	N/A
Nickel carbonate	NiCO ₃	118.7	4.39	dec	N/A
Nickel carbonyl	Ni(CO) ₄	170.7	1.32	-19°C	43°C

Source: HSDB 2009. NR = not reported; dec = decomposes; N/A = not applicable; sub = sublimes.

posed to nickel in nickel alloys and nickel-plated materials, such as coins, steel, and jewelry, and residual nickel may be found in soaps, fats, and oils (ATSDR 1997).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, releases of nickel to the environment trended downwards from 1988 to 2003 and then increased, while releases of nickel compounds increased until 1998 but have since decreased by half. In 2007, 1,552 facilities released 8.3 million pounds of nickel, and 1,027 facilities released 30.5 million pounds of nickel compounds (TRI 2009).

Occupational exposure to nickel occurs mainly through inhalation of dust particles and fumes or through dermal contact. Nickel workers can also ingest nickel-containing dusts. Occupational exposure is common for workers involved in mining, smelting, welding, casting, spray-painting and grinding, electroplating, production and use of nickel catalysts, polishing of nickel-containing alloys, and other jobs where nickel and nickel compounds are produced or used (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 23,272 workers potentially were exposed to nickel and nickel compounds (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 507,681 workers, including 19,673 women, potentially were exposed to nickel (molecular formula unknown) (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Nickel carbonyl, nickel cyanide, nickel nitrate, and nickel nitrite are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials; nickel picrate is forbidden from transport.

Nickel carbonyl, nickel cyanide, and nickel tetracarbonyl are considered marine pollutants and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Nickel compounds are listed as mobile-source air toxics for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Nickel and its compounds are listed as hazardous air pollutants.

Prevention of Accidental Release: Threshold quantity (TQ) = 1,000 lb for nickel carbonyl.

Urban Air Toxics Strategy: Nickel compounds are identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Biosolids Rule: Limits have been established for nickel in biosolids (sewage sludge) when used or disposed of via land application, surface disposal, or incineration.

Effluent Guidelines: Nickel and nickel compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 610 µg/L for metallic nickel; based on fish or shellfish consumption only = 4,600 µg/L for metallic nickel.

Numerous nickel compounds are designated as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for nickel, nickel ammonium sulfate, nickel chloride, nickel nitrate, and nickel sulfate; 10 lb for nickel carbonyl, nickel cyanide, and nickel hydroxide.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nickel and nickel compounds are listed substances subject to reporting requirements.

Threshold planning quantity (TPQ) = 1 lb for nickel carbonyl.

Reportable quantity (RQ) = 10 lb for nickel carbonyl.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nickel or nickel compounds = P073, P074, F006.

Nickel and nickel compounds are listed as hazardous constituents of waste.

Food and Drug Administration (FDA)

Maximum permissible level of nickel in bottled water = 0.1 mg/L.

The color additives ferric ammonium ferrocyanide and ferric ferrocyanide, when used in drugs, may contain nickel at levels no greater than 200 ppm.

Menhaden oil may contain nickel at concentrations not to exceed 0.5 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 mg/m³ for elemental nickel and compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value - time-weighted average (TLV-TWA) = 1.5 mg/m³ for elemental nickel; = 0.1 mg/m³ for soluble inorganic nickel compounds and nickel subsulfide; = 0.2 mg/m³ for insoluble inorganic nickel compounds; = 0.05 ppm for nickel carbonyl.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.015 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 0.001 ppm (0.007 mg/m³) for nickel carbonyl.

Immediately dangerous to life and health (IDLH) limit = 10 mg/m³ for elemental nickel and nickel compounds other than nickel carbonyl; = 2 ppm [14 mg/m³] for nickel carbonyl.

Metallic nickel and nickel compounds are listed as potential occupational carcinogens.

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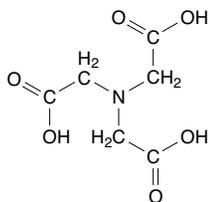
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Nitrilotriacetic Acid

CAS No. 139-13-9

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Nitrilotriacetic acid is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to nitrilotriacetic acid caused urinary-tract tumors in mice and rats. Mice and rats of both sexes were administered nitrilotriacetic acid in the diet, both as the free acid and as the trisodium salt, and male rats were administered the trisodium salt in drinking water. These exposures increased the incidences of benign or malignant tumors of the kidney, ureter, and urinary bladder; tumor types observed included tubular-cell adenoma and adenocarcinoma of the kidney and transitional-cell carcinoma of the kidney, ureter, and urinary bladder. Exposure to the free acid caused benign and/or malignant kidney tumors in mice of both sexes and in male rats, cancer of the ureter in male rats, and cancer of the urinary-bladder in female rats. Exposure to the trisodium salt had the same effects in rats and also caused kidney tumors and cancer of the ureter in female rats (NCI 1977, Goyer *et al.* 1981).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to nitrilotriacetic acid.

Properties

Nitrilotriacetic acid is a tertiary amino-polycarboxylic acid chelating agent that exists as a white crystalline powder at room temperature (HSDB 2009, NCI 1977). It is slightly soluble in water and deuterated dimethyl sulfoxide, soluble in ethanol, and insoluble in most other organic solvents. It forms water-soluble complexes with many metals and reacts with strong oxidizing compounds (IARC 1990). Physical and chemical properties of nitrilotriacetic acid are listed in the following table.

Property	Information
Molecular weight	191.1 ^a
Specific gravity	> 1 at 20°C (solid) ^a
Melting point	242°C decomposes ^a
Log K_{ow}	-3.81 ^b
Water solubility	59 g/L at 25°C ^a
Vapor pressure	7×10^{-9} mm Hg at 25°C ^b
Dissociation constant (pK_a)	3.03 at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Nitrilotriacetic acid has many commercial applications, but is used primarily as a metal ion chelating agent and as a laundry detergent builder (IARC 1990). It sequesters magnesium and calcium ions present in hard water, thereby reducing buildup and scaling caused by salts of these ions. In the late 1960s, nitrilotriacetic acid generally replaced phosphates in commercial detergents (NCI 1977). The use of nitrilotriacetic acid in detergents was suspended in the United States in 1971, but was resumed in the 1980s after phosphates were banned from detergents (HSDB 2009). Nitrilotriacetic acid also is used as an eluting agent in the purification of rare-earth elements, as a boiler feed water additive, in water and textile treatment, in metal plating and cleaning, and in pulp and paper processing (NCI 1977, IARC 1990). To a lesser extent, it is used in leather tanning, photographic development, synthetic rubber production, pharmaceutical manufacturing, and agricultural herbicide formulations and micronutrient solutions (NCI 1977). It has also been evaluated as a soil additive in the phytoremediation of heavy-metal-contaminated soil (Evangelou *et al.* 2007); chelation of the metals with nitrilotriacetic acid mobilizes them for more rapid uptake by plants.

Production

Nitrilotriacetic acid was first synthesized in 1862, and commercial production began in Europe in the 1930s (IARC 1990). In 1970, before its use in detergents was suspended, 150 million pounds of nitrilotriacetic acid was produced and used in the United States, of which 86% to 92% was used in detergents (NCI 1977). In the early 1980s, most of the annual U.S. production (approximately 66 million pounds) was exported (IARC 1990). In 2009, nitrilotriacetic acid was produced by 17 manufacturers worldwide, but none in the United States (SRI 2009), and was available from 31 suppliers, including 13 U.S. suppliers (ChemSources 2009). No current data on U.S. imports or exports of nitrilotriacetic acid were found. Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of nitrilotriacetic acid totaled 500,000 lb to 1 million pounds in 1986 and 1998, 1 million to 10 million pounds in 1990, and 10,000 to 500,000 lb in 1994 and 2000 (EPA 2004).

Exposure

The routes of potential human exposure to nitrilotriacetic acid are inhalation, ingestion, and dermal contact (HSDB 2009). The general population may be exposed through ingestion of drinking water or dermal contact with products containing nitrilotriacetic acid or its salts. Assessments of exposure to nitrilotriacetic acid were conducted in the United States in 1979, 1980, and 1985 and in Canada in 1996. These surveys assessed exposure from drinking water, bathing, wearing clothing washed with detergents containing nitrilotriacetic acid, contacting wash water, and ingesting residues remaining on hand-washed dishes. All of these studies concluded that the total daily exposure to consumers from all sources was less than 1 µg/kg of body weight per day (IARC 1999).

In 1988, EPA's Toxics Release Inventory reported environmental releases of 13,000 lb of nitrilotriacetic acid, of which 20% was released to air, 40% to surface water, and 40% to on-site landfills (TRI 2009). From 1988 to 1996, annual releases declined to a low of 1,600 lb. Since 1999, releases have ranged from 2,900 lb in 2000 to almost 64,000 lb in 2007, released by four industrial facilities. Most of the 2007 releases were to landfills, but almost 2,500 lb was released to an underground injection well.

When released to air, nitrilotriacetic acid will exist mostly in particulate form and will be removed by wet and dry deposition (HSDB

2009). In surface water, it will not volatilize or bioaccumulate in aquatic organisms; it will exist in ionized form and will likely remain in the water until biodegradation occurs, with a half-life of 0.34 to 15 days. Mean concentrations of nitrilotriacetic acid in surface water ranged from less than 0.5 to 6.4 mg/L in German rivers and lakes (Schmidt *et al.* 2004). In Canada, typical concentrations in ground and drinking water were 1 to 5 µg/L, and concentrations in Canadian environmental water samples ranged from 0.006 to 3.2 mg/L (Rakshit 2002). In Canada and Switzerland, nitrilotriacetic acid makes up about 15% of laundry detergents; the load in raw wastewater was measured at 2,500 µg/L in Canada and 100 to 1,000 µg/L in Switzerland (Bucheli-Witschel and Egli 2001). In well-adapted activated sludge systems, nitrilotriacetic acid is readily biodegraded. In soil, it is likely to biodegrade under aerobic conditions and moderate temperatures (HSDB 2009).

Occupational exposure to nitrilotriacetic acid may occur through inhalation and dermal contact during the manufacture of the compound or its salts, during water treatment, and during other procedures in which nitrilotriacetic acid is used. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 13,454 workers potentially were exposed to nitrilotriacetic acid, trisodium salt (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 25,216 workers potentially were exposed to nitrilotriacetic acid and 249,479 workers potentially were exposed to its trisodium salt (NIOSH 1990). In 1990, it was estimated that approximately 2,600 workers potentially were exposed to nitrilotriacetic acid salts during production and detergent formulation; the potential for exposure was highest for workers loading hopper cars (IARC 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

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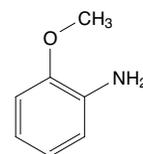
o-Nitroanisole

CAS No. 91-23-6

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)

Also known as 2-nitroanisole



Carcinogenicity

o-Nitroanisole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *o*-nitroanisole caused tumors in two rodent species and at several different tissue sites. In rats of both sexes, dietary administration of *o*-nitroanisole caused mononuclear-cell leukemia and increased the combined incidences of benign and malignant tumors of the urinary bladder, kidney, and large intestine (NTP 1993, IARC 1996). In mice, it caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma and hepatoblastoma) in males and benign liver tumors (hepatocellular adenoma) in females (NTP 1993).

Studies on Mechanisms of Carcinogenesis

Orally administered *o*-nitroanisole is metabolized predominantly to *o*-nitrophenol, which is conjugated to sulfate or glucuronide and eliminated in the urine. Less than 1% of *o*-nitroanisole is metabolized to *o*-anisidine, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. Dietary administration of *o*-anisidine hydrochloride caused tumors of the urinary bladder (transitional-cell neoplasia) in mice and rats and the kidney (transitional-cell carcinoma of the renal pelvis) in rats. *o*-Nitroanisole causes genetic damage in a wide variety of bacterial and *in vitro* mammalian test systems (NTP 1993, IARC 1996).

Since *o*-nitroanisole was listed in the *Eighth Report on Carcinogens*, additional studies relevant to mechanisms of carcinogenesis have been identified. *In vitro*, *o*-nitroanisole is metabolized by O-demethylation to 2-nitrophenol, which is oxidized to 2,5-dihydroxynitrobenzene and 2,6-dihydroxynitrobenzene (Miksanova *et al.* 2004a,b, Stiborova *et al.* 2004, Dracinska *et al.* 2006). *o*-Nitroanisole is also metabolized by nitroreduction to the DNA-reactive products 2-anisidine and *N*-(2-methoxyphenyl)hydroxylamine. DNA adducts similar to those found *in vitro* were found in the urinary bladder, liver, kidney, and spleen of male rats following intraperitoneal injection with *o*-nitroanisole. There is no evidence to suggest that mecha-

nisms by which o-nitroanisole causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to o-nitroanisole.

Properties

o-Nitroanisole is a colorless to yellowish liquid at room temperature. It is slightly soluble in water and soluble in alcohol and ether. It is stable under normal temperatures and pressures but is explosively reactive with sodium hydroxide and zinc (Akron 2009, HSDB 2009). Physical and chemical properties of o-nitroanisole are listed in the following table.

Property	Information
Molecular weight	153.1 ^a
Specific gravity	1.254 at 20°C/4°C ^a
Melting point	9.4°C ^a
Boiling point	277°C ^a
Log K _{ow}	1.73 ^a
Water solubility	1.690 g/L at 30°C ^a
Vapor pressure	3.6 × 10 ⁻³ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

o-Nitroanisole is used primarily as a precursor for o-anisidine, which is produced through direct nitroreduction (NTP 1993). o-Anisidine is used extensively in the synthesis of over 100 azo dyes, either directly after being converted to a diazonium salt or as a precursor for dianisidine, which is diazotized and coupled. o-Nitroanisole has also been used as an intermediate in pharmaceutical production (IARC 1996).

Production

o-Nitroanisole is produced by treatment of 2-chloronitrobenzene with sodium methoxide under heat and pressure. The product separates as an oil after dilution with water (IARC 1996). In 2009, o-nitroanisole was produced by two manufacturers in India (SRI 2009) and was available from 17 suppliers worldwide, including 9 U.S. suppliers (ChemSources 2009). U.S. imports of o-nitroanisole totaled over 700,000 lb in 1976 and 540,000 lb in 1978 (HSDB 2009). No more recent data on U.S. imports or exports of o-nitroanisole were found.

Exposure

The routes of potential human exposure to o-nitroanisole are dermal contact, ingestion, and inhalation. o-Nitroanisole may be released into the environment by dye and pharmaceutical manufacturing facilities through various waste streams (HSDB 2009). When released to air, o-nitroanisole will remain in the vapor phase and will be degraded by reactions with photochemically produced hydroxyl radicals, with an estimated half-life of 109 hours. When released to water, it may adsorb to sediments and suspended solids. Volatilization is very slow, with a half-life of 105 days in a model river and 772 days in a model pond. When released to soil, o-nitroanisole has moderate mobility. It is not expected to bioaccumulate in aquatic organisms. o-Nitroanisole has been identified in drinking water, but no concentrations have been reported. Occupational exposure is associated with the widespread use of o-nitroanisole in the manufacture of azo dyes (NTP 1993); however, no estimates of occupational exposure to o-nitroanisole were found.

Regulations

Department of Transportation (DOT)

o-Nitroanisole is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of o-nitroanisole is subject to certain provisions for the control of volatile organic compound emissions.

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Nitroarenes (Selected)

Introduction

The nitroarenes are a large class of structurally related chemicals normally found in particulate emissions from many combustion sources, most notably, diesel exhausts. These molecules are nitro-substituted derivatives of polycyclic aromatic hydrocarbons (arenes) with at least one nitro group covalently bound to a cyclic carbon atom (i.e., nitro-polycyclic aromatic hydrocarbons, or nitro-PAHs) (Rosenkratz and Mermelstein 1985, Tokiwa and Ohnishi 1986). The nitroarenes result from incomplete combustion processes from sources such as kerosene heaters and fuel gas burners, in addition to diesel engines. Profiles for the following listed nitroarenes follow this introduction:

- 1,6-Dinitropyrene
- 1,8-Dinitropyrene
- 6-Nitrochrysene
- 1-Nitropyrene
- 4-Nitropyrene

Following are brief discussions of carcinogenicity and exposure for nitroarenes in general. Additional information on carcinogenicity and exposure specific to each of the five listed nitroarenes is provided in the individual profiles.

These nitroarene compounds were first listed in the *Eighth Report on Carcinogens* (1998) as *reasonably anticipated to be human carcinogens* based on evidence of carcinogenicity from studies in experimental animals. Few members of this large class of chemicals have

been rigorously evaluated in state-of-the-art cancer studies in rodents. Typically, the chemicals were administered by injection, over short periods, and with less-than-optimal time allowed for tumors to fully develop. Despite these limitations, the results of carcinogenicity studies of nitroarenes in animals were generally similar and demonstrated tumor formation both at the site of injection and at distant tissue sites. The mutagenic and carcinogenic properties of the nitroarene compounds vary. The mutagenicity of nitropyrenes in *Salmonella typhimurium* strains TA98 and TA98NR increased as the number of nitro groups increased (NTP 1999). The order of mutagenic potency in human cells, from most potent to least potent, was 1,6-dinitropyrene, followed by 1,8-dinitropyrene, followed by 1-nitropyrene (Durant 1996), and levels of DNA binding in the rat mammary gland were higher for 4-nitropyrene than for 1-nitropyrene (Chae *et al.* 1997).

The metabolic pathways for activation of these nitroarene molecules to create reaction products with the ability to cause gene mutations or changes in the structure of DNA have been described in tissues from humans and animals. The metabolic pathways are similar for the five listed nitroarenes. Two successive nitroreduction steps form an *N*-hydroxylamine group. This intermediate may be activated by loss of the *N*-hydroxyl group or by *O*-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to form the DNA-reactive nitrenium ion, or it may be inactivated by further reduction to an amine. No adequate studies of the relationship between exposure to these chemicals and human cancer have been reported. However, exposure to diesel exhaust particulates is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* based on findings of elevated lung-cancer rates in occupational groups exposed to diesel exhaust and on supporting studies of cancer in experimental animals and studies on mechanisms of carcinogenesis. Whether the nitroarenes are responsible for or contribute to the carcinogenicity of diesel exhaust in humans has not been determined.

Nitroarenes are products of incomplete combustion in the presence of nitrating species (IPCS 2003). They have been identified in extracts of particles from the exhaust of diesel engines (IARC 1989). Nitroarene concentrations measured in diesel-exhaust extracts were higher for heavy-duty engines during operation and lower for engines at idle (IARC 1989, Yamazaki *et al.* 2000). Nitroarenes have also been identified in particulate matter from the incineration of municipal waste, coal fly ash, extracts of coke-oven emissions, and stack emissions from a facility manufacturing carbon electrodes. Concentrations of nitroarenes in ambient air are higher in heavily industrialized areas than in nonindustrialized urban areas, suburban areas, or rural areas (IARC 1989) and vary seasonally and diurnally. Higher concentrations in winter reflect increased emissions from heating sources, and diurnal variations reflect traffic patterns (IPCS 2003).

Because nitroarenes emitted to air are tightly bound to particulate matter, they may be removed from the atmosphere by wet and dry deposition and deposited on soil or surface water by settling and by precipitation. In Japan, all five listed nitroarenes were detected in particulates derived from coal burning (Taga *et al.* 2005) and in precipitation (Murahashi *et al.* 2001). Nitroarenes have been found in the indoor environment in particulate emissions from kerosene heaters and gas burners used for home heating and cooking (IPCS 2003). Before 1980, considerable amounts of all five listed nitroarenes were found in samples of carbon black that was known to be used in photocopiers. Some nitroarene compounds have also been identified in food products, especially in smoked and grilled meats, and in beverages, especially tea (IARC 1989).

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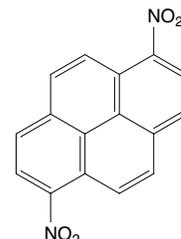
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1,6-Dinitropyrene

CAS No. 42397-64-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,6-Dinitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,6-Dinitropyrene caused tumors in several rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,6-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused benign and malignant liver tumors (adenoma and carcinoma) in male mice and cancer of the peritoneal cavity (sarcoma) in female rats (IARC 1989, Iizasa *et al.* 1993). Intrapulmonary instillation of 1,6-dinitropyrene caused lung cancer (squamous-cell carcinoma) in male rats (IARC 1989, Iwagawa *et al.* 1989), and intratracheal instillation caused lung cancer (adenocarcinoma) and myeloid leukemia in hamsters of both sexes (IARC 1989). Administration of 1,6-dinitropyrene to female rats by stomach tube caused cancer of the pituitary gland (carcinoma) (IARC 1989, Imaida *et al.* 1991).

Studies on Mechanisms of Carcinogenesis

Pathways of 1,6-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been

described (IARC 1989). Furthermore, 1,6-dinitropyrene-induced tumors showed evidence of oncogene activation and mutations (Ishizaka *et al.* 1987, Smith *et al.* 1997). The potential modes of action in the carcinogenicity of 1,6-dinitropyrene therefore involve metabolic activation to reactive metabolites, oncogene activation, and genotoxicity.

The mutagenicity of 1,6-dinitropyrene is related to the ability of its metabolites to bind DNA. Reactive products of 1,6-dinitropyrene are formed by metabolism through two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxy amino group at the 1-position. Activation occurs by O-acetylation of the *N*-hydroxylamine group, followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct. Both nitroreduction and acetylation dependent on acetyl coenzyme A are involved in the metabolism of 1,6-dinitropyrene to form the DNA adduct *N*-(deoxyguanosin-8-yl)-1-amino-6-nitropyrene (Beland 1986). This adduct forms in a dose-related manner in the liver, mammary gland, peripheral-blood lymphocytes, kidney, urinary bladder, and spleen lymphocytes of rats exposed to 1,6-dinitropyrene (Beland 1986, 1994, El-Bayoumy *et al.* 1994, Smith *et al.* 1995). Exposure of SV40-transformed hamster ovary cells to 1,6-dinitropyrene also caused formation of DNA adducts and amplified SV40 DNA (Neft 1993).

1,6-Dinitropyrene was genotoxic in a wide variety of assays in bacteria and mammalian cells, including human cells (IARC 1989). The most frequent mutations in *Salmonella typhimurium* were C:G to A:T or G:C transversions (Watanabe *et al.* 1997). Another metabolite of 1,6-dinitropyrene, 1-nitroso-6-nitropyrene, caused frame-shift mutations at G:C base pairs in the *lacI* gene of *Escherichia coli* (Lambert *et al.* 1998, 2001). Intrapulmonary administration of single doses of 1,6-dinitropyrene that caused dose-dependent induction of lung tumors in rats also resulted in dose-dependent formation of DNA adducts in the lungs and liver and mutations in lymphocytes (Beland *et al.* 1994, Smith *et al.* 1995). Intratracheal administration of 1,6-dinitropyrene to *gpt*-delta transgenic mice induced mutations in the lungs (Hashimoto *et al.* 2006). Mutations in the *K-ras* proto-oncogene and *p53* tumor-suppressor gene were observed in 1,6-dinitropyrene-induced lung tumors and in the *hprt* gene of 6-thioguanine-resistant lymphocytes in rats exposed to 1,6-dinitropyrene. In the lung tumors, mutations were identified in *K-ras* codon 12 (5 mutations in 20 tumors) and *p53* exons 3, and 5 to 8 (9 of 20 tumors) and were mainly substitutions at G:C base pairs (Smith *et al.* 1997). Another study in rats reported that *H-ras* and *N-ras* were activated in 18% of 1,6-dinitropyrene-induced fibrosarcomas (Ishizaka *et al.* 1987).

In addition to gene mutations, 1,6-dinitropyrene caused DNA damage, induction of unscheduled DNA synthesis, sister chromatid exchange, and chromosomal damage in cultured cells. It also caused morphological transformation of rat tracheal cells (IARC 1989, NTP 1999). Moreover, *in vivo* exposure to 1,6-dinitropyrene transformed immortalized human bronchial epithelial cells (BEAS-2B) into malignant lung tumors (adenocarcinoma). The BEAS-2B cells were xenotransplanted into de-epithelialized rat tracheas, which were transplanted under the dorsal skin of nude mice and exposed to 1,6-dinitropyrene. The tumor cells did not contain the usual molecular genetic abnormalities found in lung adenocarcinoma (i.e., mutations in the *K-ras*, *p53*, or *Rb* genes), suggesting that other molecular alterations involving different oncogenes, tumor-suppressor genes, or growth-factor-related genes may have been responsible for transformation of the BEAS-2B cells. There is no evidence to suggest that mechanisms by which 1,6-dinitropyrene causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,6-dinitropyrene.

Properties

1,6-Dinitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow to light-brown crystalline solid. It has a molecular weight of 292.3 and a melting point of 310°C. It is practically insoluble in water but moderately soluble in toluene (IARC 1989, IPCS 2003, HSDB 2009, Akron 2010).

Use

There is no evidence that 1,6-dinitropyrene has been used for any commercial purpose (IARC 1989). 1,6-Dinitropyrene is available for research purposes at a purity of 98% or higher. It is also available in ¹⁴C- or ³H-labeled form at a radiochemical purity of 98% or higher.

Production

One non-U.S. company was previously reported to synthesize 1,6-dinitropyrene at a purity higher than 99.9% (IARC 1989). In 2009, no commercial producers of 1,6-dinitropyrene were identified worldwide, but 1,6-dinitropyrene was available from four U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,6-dinitropyrene were found.

Exposure

The primary route of human exposure to 1,6-dinitropyrene is inhalation (IARC 1989). 1,6-Dinitropyrene was measured in diesel exhaust particulate extracts at concentrations of 1.2 mg/kg for heavy-duty engines during operation and up to 2.4 pmol/mg (0.7 mg/kg) for diesel engines at idle (IARC 1989, Yamazaki *et al.* 2000). 1,6-Dinitropyrene was measured in particulates derived from coal-burning at a concentration of 0.26 pmol/mg (0.08 mg/kg) (Taga *et al.* 2005). Concentrations measured in ambient air were higher in heavily industrialized areas (7.5 pg/m³) than in nonindustrialized urban areas (0.48 pg/m³), suburban areas (0.30 pg/m³), or rural areas (0.12 pg/m³) (IARC 1989). In Japan, 1,6-dinitropyrene was measured in precipitation at concentrations of up to 0.04 pmol/L (Murahashi *et al.* 2001) and in soil samples from various regions of the country at concentrations of 3 ng/g or less (Watanabe *et al.* 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,6-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 1,6-dinitropyrene were identified.

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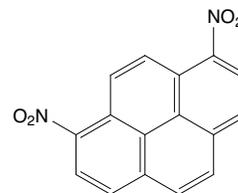
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1,8-Dinitropyrene

CAS No. 42397-65-9

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,8-Dinitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,8-Dinitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,8-dinitropyrene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1989). Exposure by intraperitoneal injection caused myelocytic leukemia and cancer of the peritoneal cavity (sarcoma) and mammary gland (adenocarcinoma) in female rats. Administration of 1,8-dinitropyrene to female rats by stomach tube also caused mammary-gland cancer (adenocarcinoma).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1,8-dinitropyrene.

Studies on Mechanisms of Carcinogenesis

Pathways of 1,8-dinitropyrene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been described (IARC 1989). Reactive products of 1,8-dinitropyrene are formed by metabolism through two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxy amino group at the 1-position (Beland 1986). Activation occurs by *O*-acetylation of the *N*-hydroxylamine group followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct.

1,8-Dinitropyrene is genotoxic in a wide variety of assays in bacteria and mammalian cells (IARC 1989). In *Salmonella typhimurium*, the most frequent mutations were C:G to A:T or G:C transversions (Watanabe *et al.* 1997), and a metabolite of 1,8-dinitropyrene, 1-nitroso-8-nitropyrene, caused mutations at G:C base pairs and frameshift mutations (Lambert *et al.* 2001). 1,8-Dinitropyrene also caused morphological transformation of cultured hamster embryo cells (IARC 1989). Exposure of SV40-transformed hamster ovary cells to 1,8-dinitropyrene caused formation of DNA adducts and amplified SV40 DNA (Neft 1993).

There is no evidence to suggest that the mechanisms by which 1,8-dinitropyrene causes tumors in experimental animals would not also operate in humans.

Properties

1,8-Dinitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow fluffy or light-brown

crystalline solid (IARC 1989). It has a molecular weight of 292.3 and a melting point of over 300°C (HSDB 2009).

Use

1,8-Dinitropyrene has been reported to be a photosensitizer; however, there is no evidence that it has ever been used commercially for this or any other purpose (IARC 1989). 1,8-Dinitropyrene is available for research purposes at a purity of at least 99% and in ¹⁴C- or ³H-labeled form at a radiochemical purity of at least 98%.

Production

In 2009, no commercial producers of 1,8-dinitropyrene were identified worldwide, but 1,8-dinitropyrene was available from two U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,8-dinitropyrene were found.

Exposure

The routes of human exposure to 1,8-dinitropyrene are inhalation, ingestion, and dermal contact (IARC 1989). In Japan, 1,8-dinitropyrene was detected in soil samples in various regions of the country (Watanabe *et al.* 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,8-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 1,8-dinitropyrene were identified.

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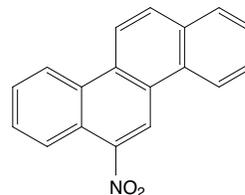
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6-Nitrochrysene

CAS No. 7496-02-8

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

6-Nitrochrysene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

6-Nitrochrysene caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Intraperitoneal injection of 6-nitrochrysene caused malignant lymphoma and benign or malignant tumors of the lung (adenoma of adenocarcinoma) and liver (hepatocellular adenoma or carcinoma) in mice of both sexes (Busby *et al.* 1989, IARC 1989, El-Bayoumy *et al.* 1992, Imaida *et al.* 1992, Fu *et al.* 1994, Li *et al.* 1994). In newborn rats, intraperitoneal injection of 6-nitrochrysene caused benign or malignant colon tumors (adenoma or adenocarcinoma) in both sexes (Imaida *et al.* 1992). Injection of 6-nitrochrysene directly into the mammary gland of 30-day-old female rats caused benign and malignant tumors of the mammary gland (fibroadenoma, adenocarcinoma, and spindle-cell sarcoma) (El-Bayoumy *et al.* 1993).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 6-nitrochrysene.

Studies on Mechanisms of Carcinogenesis

In an initiation-promotion study using a phorbol ester as a tumor promoter, 6-nitrochrysene induced mainly benign skin tumors (papilloma) (El-Bayoumy *et al.* 1982). When given by intraperitoneal injection to transgenic mice carrying a human hybrid *c-Ha-ras* gene, 6-nitrochrysene caused lung and forestomach tumors (Ogawa *et al.* 1996). Injection of 6-nitrochrysene metabolites (1,2-dihydroxy-1,2-dihydro-6-nitrochrysene, 6-aminochrysene, 1,2-dihydroxy-3,4-epoxy-1,2,3,4-tetrahydro-6-nitrochrysene, or 1,2-dihydroxy-1,2-dihydro-6-aminochrysene) directly into the mammary gland of 30-day-old female rats caused cancer of the mammary gland (adenocarcinoma) (El-Bayoumy *et al.* 2002), but none of the metabolites was as potent as 6-nitrochrysene.

Pathways of 6-nitrochrysene metabolism leading to mutagenic and carcinogenic metabolites have been described (El-Bayoumy *et al.* 2002). Two different DNA-reactive metabolites are formed by two different pathways; however, an intermediate product in the second pathway can also feed into the first pathway (Li *et al.* 1994). One pathway involves ring hydroxylation followed by nitroreduction to form *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysene, which can form a DNA-reactive epoxide (1,2-dihydro-1,2-dihydroxy-6-aminochrysene-3,4-epoxide). The other pathway is similar to that which activates 1,6-dinitropyrene, 1,8-dinitropyrene, and 1-nitropyrene; it proceeds

by two steps of nitroreduction to form *N*-hydroxy-6-aminochrysenes, which can then react with deoxyguanosine or deoxyadenosine to form at least three different DNA adducts. *N*-hydroxy-6-aminochrysenes can also be ring hydroxylated to form *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysenes, the precursor of the 3,4-epoxide in the first pathway. 6-Nitrochrysenes–DNA adducts were detected in tumor target tissues (lung, liver, colon, and mammary gland) in rats exposed to 6-nitrochrysenes, and adducts of its metabolites were found in cells from target tissues exposed *in vitro*. Moreover, 6-nitrochrysenes adducts caused mutations in the *hprt* gene of Chinese hamster ovary cells, mostly at A:T base pairs (Manjanatha *et al.* 1996). 6-Nitrochrysenes was genotoxic in several assays in bacteria and mammalian cells and caused morphological transformation of finite-lifespan cells *in vitro* (IARC 1989).

In 6-nitrochrysenes–induced mammary-gland tumors from female transgenic rats (Big Blue F344 × Sprague–Dawley F₁), the types of mutations observed (mainly A:T to G:C or T:A base-pair mutations) were consistent with the structure of 6-nitrochrysenes–DNA adducts detected in this target organ (Boyiri *et al.* 2004). The metabolite with a mutational profile most similar to that of 6-nitrochrysenes was *trans*-1,2-dihydroxy-1,2-dihydro-*N*-hydroxy-6-aminochrysenes, which arises from both ring oxidation and nitroreduction (Guttenplan *et al.* 2007). Mutations in the *K-ras* proto-oncogene (involving C:G and A:T base pairs at codons 12, 13, and 61) were found in lung tumors (adenoma and adenocarcinoma) induced by 6-nitrochrysenes or some of its metabolites, such as *trans*-1,2-dihydro-1,2-dihydroxy-6-aminochrysenes, which is consistent with a role for the major adduct formed by this metabolite in formation of these tumors (Li *et al.* 1994). These findings support the possibility that the tumors caused by 6-nitrochrysenes are at least in part a result of DNA damage. There is no evidence to suggest that mechanisms by which 6-nitrochrysenes causes tumors in experimental animals would not also operate in humans.

Properties

6-Nitrochrysenes is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as chrome-red to light-yellow to orange-yellow needles or prism-shaped crystals. It has a molecular weight of 273.3 and a melting point of 209°C, and it sublimes without decomposition. It is practically insoluble in water; slightly soluble in cold ethanol, diethyl ether, and carbon disulfide; slightly more soluble in benzene and acetic acid; and soluble in hot nitrobenzene (IARC 1989, WHO 2003).

Use

There is no evidence that 6-nitrochrysenes has been used commercially for any purpose. 6-Nitrochrysenes is used as an internal standard in the chemical analysis of nitroarenes (IARC 1989). It is available for research purposes at a purity of at least 98% and as a reference material at a certified purity of 98.9%.

Production

6-Nitrochrysenes was first synthesized in 1890 (IARC 1989). In 2009, no commercial producers of 6-nitrochrysenes were identified worldwide, but 6-nitrochrysenes was available from three U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 6-nitrochrysenes were found.

Exposure

The routes of human exposure to 6-nitrochrysenes are inhalation, ingestion, and dermal contact. 6-Nitrochrysenes was measured in diesel exhaust particulate extracts at a concentration of 0.78 µg/g

(0.78 mg/kg) for heavy-duty engines during operation (IPCS 2003). The median concentration of hemoglobin adducts of 6-nitrochrysenes measured in the blood of 29 bus-garage workers as an indicator of personal exposure to diesel exhaust was the same as in the control groups of urban and rural residents (Zwirner-Baier and Neumann 1999). No data were found on occupational exposure to 6-nitrochrysenes. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 6-nitrochrysenes were identified.

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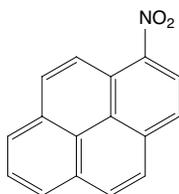
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1-Nitropyrene

CAS No. 5522-43-0

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1-Nitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1-Nitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. It caused benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) in 30-day-old female rats, in newborn male and female rats exposed by stomach tube (El-Bayoumy *et al.* 1995), and in female rats exposed by intraperitoneal or subcutaneous injection (IARC 1989). Subcutaneous injection of 1-nitropyrene also caused cancer at the injection site (sarcoma) in rats of both sexes. Lung tumors were observed in male hamsters exposed by intratracheal instillation (1-nitropyrene was adsorbed on carbon-black particles) (Moon *et al.* 1990) and in female strain A/J mice and newborn male CD-1 mice exposed by intraperitoneal injection (IARC 1989). In the A/J mice (a strain with a high spontaneous rate of lung tumors), both tumor incidence and the number of tumors per mouse were increased. In the newborn CD-1 mice, 1-nitropyrene also caused benign or malignant liver tumors (adenoma or carcinoma).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 1-nitropyrene.

Studies on Mechanisms of Carcinogenesis

A DNA-binding metabolite of 1-nitropyrene is responsible for its genotoxic effects. 1-Nitropyrene is metabolized by two reductions of the 1-nitro group to form first a nitroso and then a *N*-hydroxylamine group at the 1-position (Beland 1986). Activation occurs by loss of the *N*-hydroxyl group or by *O*-acetylation of the *N*-hydroxylamine group, followed by removal of the acetate, either of which creates the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct. 1-Nitropyrene formed DNA adducts *in vitro* and *in vivo* and was genotoxic in a wide variety of assays in bacteria and mammalian cells, including human cells and cells from likely target tissue sites (IARC 1989). In particular, DNA adducts were detected in the lung following intratracheal instillation of 1-nitropyrene, indicating potential genotoxic activity in a likely target organ in humans (IARC 1989, NTP 1996, 1999). 1-Nitropyrene also consistently caused morphological transformation of both finite-life-span and immortal cell lines, including human cells. 1-Nitropyrene transformed rat tracheal epithelial cells *in vivo* following intratracheal administration, but not *in vitro*, suggesting that metabolic activation not present in the tracheal cells might be necessary for transforma-

tion (Ensell *et al.* 1998). Furthermore, subcutaneous injection with cell lines established from the transformed rat tracheal epithelial cells caused malignant tumors (squamous-cell carcinoma) in nude mice (Ensell *et al.* 1999). There is no evidence to suggest that mechanisms by which 1-nitropyrene causes tumors in experimental animals would not also operate in humans.

Properties

1-Nitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists as yellow needles or prisms at room temperature. It is practically insoluble in water; very soluble in diethyl ether, and soluble in ethanol, benzene, toluene, and tetrahydrofluorenone (IARC 1989, HSDB 2010). It is stable under normal temperatures and pressures, but decomposes following exposure to ultraviolet or visible light (Akron 2010, IARC 1989). Physical and chemical properties of 1-nitropyrene are listed in the following table.

Property	Information
Molecular weight	247.3 ^a
Melting point	155°C ^a
Log <i>K</i> _{ow}	5.06 ^a
Water solubility	0.0118 mg/L at 25°C ^b
Vapor pressure	5.52 × 10 ⁻⁸ mmHg at 25°C ^b

Sources: ^aHSDB 2010, ^bChemIDplus 2010.

Use

1-Nitropyrene has been reported to be a chemical photosensitizer, and one non-U.S. company was reported to have used it as an intermediate in the production of 1-azidopyrene, which is used in photosensitive printing. 1-Nitropyrene is available for research purposes at a purity of 97% or of greater than 99.5% with no more than 0.1% total dinitropyrenes and pyrene. It also is available as a reference material at a purity of 99.68% (IARC 1989).

Production

In 1989, one non-U.S. company was reported to produce 1-nitropyrene by the reaction of pyrene with nitric acid (IARC 1989). In 2010, no U.S. commercial producers of 1-nitropyrene were identified, but 1-nitropyrene was available from 14 suppliers worldwide, including 7 U.S. suppliers (ChemSources 2010). No data on U.S. imports or exports of 1-nitropyrene were found.

Exposure

The routes of human exposure to 1-nitropyrene are inhalation, ingestion, and dermal contact (HSDB 2010). Measurement of 1-nitropyrene in diesel exhaust has frequently been used as an indicator of the presence of over 200 different nitro-PAHs (Scheepers *et al.* 2003). 1-Nitropyrene has also been detected in the fumes from soybean cooking oil (Wu *et al.* 1998) and in dried herbs such as basil, chervil, marjoram, oregano, and sage (Spitzer *et al.* 2000). 1-Nitropyrene was measured in diesel exhaust particulate extracts at concentrations of 5.0 mg/kg for heavy-duty engines during operation, up to 93 mg/kg for a six-cylinder passenger-vehicle engine during operation, and up to 63 pmol/mg (15.6 mg/kg) for engines at idle (IARC 1989, Yamazaki *et al.* 2000, IPCS 2003). Emissions of 1-nitropyrene also depend on the composition of the diesel fuel; emissions from the same engine were much lower for Swedish diesel fuel classified as environmentally friendly (MK1) than for European Program on Emissions Fuels and Engine Technologies reference fuels (Westerholm *et al.* 2001). 1-Nitropyrene was measured in particulates derived from coal-burning at a concentration of 5.3 pmol/mg (1.3 mg/kg) (Taga *et al.* 2005).

Concentrations of 1-nitropyrene in ambient air were higher in heavily industrialized areas (0.057 ng/m³) than in non-industrialized urban areas (0.030 ng/m³), suburban areas (0.022 ng/m³), or rural areas (0.013 ng/m³) (IARC 1989). In Japan, concentrations varied from a high of 413 pg/m³ in Sapporo in winter to a low of 11.3 pg/m³ in Kanazawa in summer at night. In Japan, 1-nitropyrene was detected in precipitation and at low concentrations in river water and lower concentrations in seawater on the days after precipitation (Murahashi *et al.* 2001). 1-Nitropyrene has also been detected in soil, sewage sludge, sediment, and incinerator ash (IPCS 2003). It is expected to be immobile in soil (HSDB 2010).

The median concentration of hemoglobin adducts of 1-nitropyrene measured in the blood of 29 bus-garage workers as an indicator of personal exposure to diesel exhaust was 0.13 pmol/g hemoglobin, which was lower than in the control group of urban residents (0.16 pmol/g) and higher than in rural residents (0.10 pmol/g) (Zwirner-Baier and Neumann 1999). The concentration of 1-nitropyrene in lung-tissue specimens collected in Fukuoka, Japan, from 1991 to 1996 was 19.7 ± 10.5 pg/g of dry weight, which was lower than in lung specimens collected from 1961 to 1962, a period of heavy air pollution (Tokiwa *et al.* 1998).

Occupational exposure to 1-nitropyrene was documented for operators of diesel-powered machinery used in mining (IPCS 2003). In an oil-shale mine in Estonia, concentrations of 1-nitropyrene in respirable dust were much higher for underground than surface operations (Scheepers *et al.* 2003). (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

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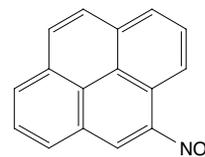
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4-Nitropyrene

CAS No. 57835-92-4

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

4-Nitropyrene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4-Nitropyrene caused tumors in two rodent species, at several different tissue sites, and by several different routes of administration. Intraperitoneal injection of 4-nitropyrene caused benign and malignant tumors of the lung in newborn mice of both sexes and of the liver in newborn male mice (IARC 1989). In female rats, it caused benign or malignant mammary-gland tumors (adenoma, fibroadenoma, or adenocarcinoma) (Imaida *et al.* 1991). In newborn female rats, subcutaneous injection of 4-nitropyrene caused cancer at the injection site (sarcoma), mammary-gland cancer (adenocarcinoma), leukemia, and Zymbal-gland tumors (IARC 1989, Imaida *et al.* 1995). Injections of 4-nitropyrene directly into the mammary gland of 30-day-old female rats caused benign or malignant mammary-gland tumors (fibroadenoma or adenocarcinoma) (Imaida *et al.* 1991, El-Bayoumy *et al.* 1993).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 4-nitropyrene.

Studies on Mechanisms of Carcinogenesis

Metabolic pathways for 4-nitropyrene include both ring oxidation and nitroreduction (Upadhyaya *et al.* 1994), resulting in mutagenic metabolites. DNA adducts were detected *in vitro* (Sun *et al.* 2004) and in the liver and mammary glands of rats exposed to 4-nitropyrene *in vivo* (Chae *et al.* 1997). Analysis of liver and mammary-gland DNA obtained from exposed rats yielded four radioactive peaks that coeluted with markers derived from the nitroreductive pathway, indicating that nitroreduction is primarily responsible for DNA adduct formation in these tissues (Chae *et al.* 1999). 4-Nitropyrene was genotoxic in bacteria and caused morphological transformation of BALB/3T3 mouse embryonic fibroblast cells *in vitro* (NTP 1999). There is no evidence to suggest that mechanisms by which 4-nitropyrene causes tumors in experimental animals would not also operate in humans.

Properties

4-Nitropyrene is a nitro-substituted polycyclic aromatic hydrocarbon that exists as orange needles at room temperature (IARC 1989). It is practically insoluble in water but soluble in organic solvents such as acetone, benzene, dimethyl sulfoxide, and methylene chloride (WHO 2003). Physical and chemical properties of 4-nitropyrene are listed in the following table.

Property	Information
Molecular weight	247.3 ^a
Melting point	190°C to 192°C ^a
Boiling point	472°C ^b
Water solubility	0.017 mg/L at 25°C ^b
Vapor pressure	3.3 × 10 ⁻⁸ mm Hg at 25°C ^b

Sources: ^aIARC 1989, ^bWHO 2003.

Use

4-Nitropyrene is used only as a laboratory chemical (IARC 1989); there is no evidence that it has ever been used for commercial purposes.

Production

4-Nitropyrene is produced only for laboratory use (IARC 1989). In 2009, no commercial producers of 4-nitropyrene were identified worldwide, but 4-nitropyrene was available from one U.S. supplier (ChemSources 2009). No data on U.S. imports or exports of 4-nitropyrene were found.

Exposure

The routes of human exposure to 4-nitropyrene are inhalation, ingestion, and dermal contact. 4-Nitropyrene was measured in diesel exhaust particulate extracts at concentrations of 0.07 µg/g (0.07 mg/kg) for heavy-duty engines during operation and up to 0.04 pmol/mg (0.01 mg/kg) for engines at idle (IPCS 2003). 4-Nitropyrene was measured in particulates derived from coal-burning at a concentration of 2.29 pmol/mg (0.57 mg/kg) (Taga *et al.* 2005). No data were found on occupational exposure to 1,6-dinitropyrene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

Regulations

No specific regulations or guidelines relevant to reduction of exposure to 4-nitropyrene were identified.

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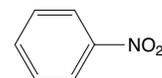
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Nitrobenzene

CAS No. 98-95-3

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

Nitrobenzene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to nitrobenzene by inhalation caused tumors at numerous tissue sites in mice and rats. In mice, inhalation exposure to nitrobenzene caused benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) and benign thyroid-gland tumors (follicular-cell adenoma) in males and benign mammary-gland tumors (adenocarcinoma) in females. In rats, it caused benign liver tumors (hepatocellular adenoma) in males of both strains tested, kidney tumors (renal adenoma) in males of one strain, and endometrial tumors (stromal polyps) in females. In addition, the incidences of benign liver tumors in female mice and rats and benign thyroid-gland tumors in male rats of one strain were marginally increased with increasing nitrobenzene exposure level (Cattley *et al.* 1994).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to nitrobenzene. The only relevant study found was a case-control study of children whose fathers were occupationally exposed to nitrobenzene. Paternal exposure was associated with a statistically

nonsignificant increase in the risk of childhood brain cancer, based on a small number of cancer patients whose fathers had been exposed to nitrobenzene (Wilkins and Sinks 1990).

Studies on Mechanisms of Carcinogenesis

Nitrobenzene did not cause mutations in bacteria, with or without mammalian metabolic activation, or genetic damage in most mammalian test systems (IARC 1996). It did not cause unscheduled DNA synthesis in cultured human or rat hepatocytes (Butterworth *et al.* 1989). Inhalation exposure of rats to nitrobenzene did not cause sister chromatid exchange in lymphocytes in the spleen or peripheral blood, chromosomal aberrations in peripheral-blood lymphocytes, or unscheduled DNA synthesis in hepatocytes (IARC 1996). However, in humans, inhalation exposure to nitrobenzene did cause chromosomal aberrations in peripheral-blood lymphocytes (Huang *et al.* 1995, 1996).

Nitrobenzene is absorbed dermally and by inhalation in both humans and experimental animals, and its metabolism appears to be similar in humans and animals. Nitrobenzene metabolites are excreted primarily in the urine. Two pathways for nitrobenzene metabolism have been proposed: (1) reduction of the nitro group to form aniline, followed by ring oxidation to form aminophenols, which can conjugate with glucuronide or sulfate, and (2) ring oxidation to form nitrophenols, which can conjugate with glucuronide or sulfate (Rickert 1987). Nitrobenzene can be reduced to aniline under anaerobic conditions (by bacteria in the intestine) or aerobic conditions (in the microsomes of mammalian cells). The former is more likely to occur when nitrobenzene is ingested, and the latter when nitrobenzene is inhaled. Reduction of nitrobenzene to aniline appears to be an important step in development of methemoglobinemia (a condition in which altered hemoglobin cannot carry oxygen) observed in humans and experimental animals exposed to nitrobenzene (IARC 1996, Holder 1999, NTP 2002). The mechanism by which nitrobenzene causes cancer has not been determined. Nitrobenzene is structurally related to other aromatic nitro and amino compounds, including several nitroarenes listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens* and classified by the International Agency for Research on Cancer as possibly carcinogenic to humans (IARC 1989).

Properties

Nitrobenzene is a nitro aromatic compound that exists at room temperature as a greenish-yellow or yellow oily liquid with the odor of bitter almonds. It is slightly soluble in water, soluble in acetone, and freely soluble in alcohol, benzene, ether, and oils. Nitrobenzene is stable when stored under normal temperatures and pressures, but has explosive potential when exposed to heat or flames, especially in the presence of strong alkalis or acids (IARC 1996). Physical and chemical properties of nitrobenzene are listed in the following table.

Property	Information
Molecular weight	123.1 ^a
Specific gravity	1.2037 at 20°C/4°C ^a
Melting point	5.7°C ^a
Boiling point	210.8°C ^a
Log K_{ow}	1.85 ^a
Water solubility	2.090 g/L at 25°C ^b
Vapor pressure	0.245 mm Hg at 25°C ^a
Vapor density relative to air	4.1 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Most nitrobenzene (97%) is used in the manufacture of aniline (IARC 1996, HSDB 2009). Miscellaneous uses include the manufacture of benzidine, quinoline, azobenzene, pyroxylin compounds, isocyanates, pesticides, rubber chemicals, pharmaceuticals, and dyes such as nigrosines and magenta. Nitrobenzene is found in soaps and shoe and metal polishes and is used as a solvent for cellulose ester, in modifying esterification of cellulose acetate, and in refining lubricating oils (HSDB 2009). Nitrobenzene also is used as a solvent in petroleum refining and the synthesis of other organic compounds, such as acetaminophen (ATSDR 1990).

Production

Nitrobenzene is produced in a continuous process by the direct nitration of benzene (IARC 1996). The demand for nitrobenzene and its U.S. production increased steadily from 73,000 metric tons (161 million pounds) in 1960 to 1,390,000 metric tons (3,064 million pounds) by 2007 (IARC 1996, Bizzari and Kishi 2007). In 1995, nitrobenzene ranked 49th in volume among chemicals produced in the United States (Kirschner 1996). In 2009, there were 5 U.S. producers and 20 U.S. suppliers of nitrobenzene (ChemSources 2009, SRI 2009). Imports and exports of nitrobenzene are reported to be negligible (ATSDR 1990, HSDB 2009).

Exposure

The general population potentially is exposed to nitrobenzene in the environment through inhalation of ambient air, ingestion of water, or dermal contact with products or water containing nitrobenzene. Two surveys, one of nearly 600 urban and suburban sites in the United States and one of more than 700 U.S. sites, reported mean concentrations of nitrobenzene in air to be 0.17 ppb and 0.117 ppb, respectively (ATSDR 1990, HSDB 2009). In a survey of 862 hazardous-waste sites, nitrobenzene was detected in groundwater at 3 sites, at a geometric mean concentration of 1.4 ng/L, but was not detected in surface-water samples from any site (ATSDR 1990).

Occupational exposure to nitrobenzene generally is by inhalation of the vapor or dermal contact with the vapor or liquid. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 5,080 workers, including 475 women, potentially were exposed to nitrobenzene (IARC 1996, HSDB 2009). No more recent data on occupational exposure to nitrobenzene were found. Direct release of nitrobenzene to air during its manufacture is minimized by passage of contaminated air through activated charcoal. Most (97% to 98%) of the nitrobenzene produced is retained in closed systems for use in synthesis of aniline and other substituted nitrobenzenes and anilines, thus limiting its release into air (ATSDR 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of nitrobenzene on ships and barges.

Department of Transportation (DOT)

Nitrobenzene is considered a hazardous material and marine pollutant, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of nitrobenzene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 17 µg/L; based on fish or shellfish consumption only = 690 µg/L.

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 1,000 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 2.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of nitrobenzene = U169, F004, K083, K103, K104.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (5 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm (5 mg/m³).

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm (5 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 200 ppm.

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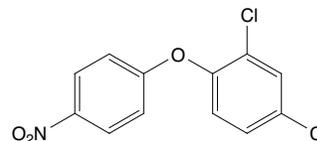
Nitrofen

CAS No. 1836-75-5

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as 2,4-dichlorophenyl-*p*-nitrophenyl ether or niclofen



Carcinogenicity

Nitrofen is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to nitrofen caused tumors in two rodent species and at two different tissue sites. Dietary administration of technical-grade nitrofen caused benign and malignant liver tumors in mice (hepatocellular adenoma and carcinoma in both sexes and hemangiosarcoma in males) and cancer of the pancreas (carcinoma) in female rats (NCI 1978, 1979, IARC 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to nitrofen.

Properties

Nitrofen (2,4-dichlorophenyl-*p*-nitrophenyl ether) is a substituted diphenyl ether which at room temperature is a white to yellow to dark brown crystalline solid (NCI 1978, HSDB 2009). It is insoluble in water, soluble in acetone, methanol, xylene, benzene, and *n*-hexane, and slightly soluble in ethanol (HSDB 2009). It darkens on exposure to light (Akron 2009). Physical and chemical properties of nitrofen are listed in the following table.

Property	Information
Molecular weight	284.1 ^a
Specific gravity	1.33 at 90°C ^a
Melting point	70°C to 71°C ^a
Boiling point	180°C to 190°C at 0.25 mm Hg ^a
Log <i>K</i> _{ow}	5.534 ^a
Water solubility	0.001 g/L at 22°C ^a
Vapor pressure	8 × 10 ⁻⁶ mm Hg at 40°C ^b

Sources: ^aHSDB 2009, ^bIARC 1983.

Use

Nitrofen has been used as a contact herbicide on a variety of food and ornamental crops for pre- and post-emergence control of annual grasses and broadleaf weeds (NCI 1979, HSDB 2009). Nitrofen was applied to crops in 25 U.S. states by growers of rice, broccoli, cauliflower, cabbage, Brussels sprouts, onions, garlic, and celery. In 1975, it was estimated that over 800,000 lb of nitrofen was used in the United States; estimated usage on crops was 904,000 lb in 1978 and remained close to that level in 1980 (IARC 1983, HSDB 2009). Nitrofen was also used in nurseries that grew roses and chrysanthemums and on roadsides, but it was not used around homes and gardens (HSDB 2009).

nant skin tumors (squamous-cell papilloma and carcinoma) in female mice (IARC 1975, 1982).

Cancer Studies in Humans

When used as an antineoplastic agent, nitrogen mustard hydrochloride usually is used in combination with other antineoplastic drugs; however, it has been used alone to treat mycosis fungoides (IARC 1975, 1982). Squamous-cell carcinoma has occurred following repeated application of nitrogen mustard hydrochloride to the skin of patients with mycosis fungoides. Cases have also been reported in which leukemia and other cancers have developed in Hodgkin's disease patients treated with drug combinations that included nitrogen mustard hydrochloride with or without radiation therapy.

Since nitrogen mustard hydrochloride was listed in the *Fourth Annual Report on Carcinogens*, additional cancer studies in humans have been identified. The International Agency for Research on Cancer reported that there was limited evidence for the carcinogenicity of nitrogen mustard hydrochloride in humans (IARC 1987). IARC noted that although there were numerous case reports of cancer following treatment with nitrogen mustard hydrochloride, the patients had also been treated with radiation or other drugs. No epidemiological studies of nitrogen mustard hydrochloride as a single agent have been published since the last IARC review. A large case-control study of lung cancer following treatment for Hodgkin's lymphoma found that lung-cancer risk increased significantly with increasing cumulative dose of mechlorethamine (nitrogen mustard hydrochloride) among patients treated with a combination of mechlorethamine, vincristine, procarbazine, and prednisone (MOPP) (*P* for trend < 0.001 for mechlorethamine evaluated separately) (Travis *et al.* 2002). The other available studies did not evaluate independent effects of nitrogen mustard hydrochloride (Franklin *et al.* 2005), did not adjust for exposure to other drugs, or were based on small numbers of exposed cases (Zaridze *et al.* 1993).

Properties

Nitrogen mustard hydrochloride is a compound analogous to mustard gas, with sulfur replaced by nitrogen. It exists at room temperature as white to off-white crystals or powder with a fishy odor. It is soluble in water and ethanol. The dry crystals are stable at room temperature, but unstable in aqueous solution (IARC 1975). Physical and chemical properties of nitrogen mustard hydrochloride are listed in the following table.

Property	Information
Molecular weight	192.5 ^a
Specific gravity	1.118 g/cm ³ at 25°C ^b
Melting point	109°C to 111°C ^a
Boiling point	87°C at 18 mm Hg ^b
Log <i>K</i> _{ow}	-1.24 ^a
Water solubility	10g/L ^a
Dissociation constant (p <i>K</i> _a)	6.43 at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The only known commercial use of nitrogen mustard is as a chemical intermediate in the production of its hydrochloride. Nitrogen mustard hydrochloride is used in limited quantities as an antineoplastic agent, either alone or in combination with other chemotherapeutic agents, to treat neoplastic diseases, including Hodgkin's disease, leukemia, generalized lymphosarcoma, mycosis fungoides, polycythemia vera, and bronchogenic carcinoma. It may also be used to treat non-Hodgkin's lymphoma, malignant melanoma, breast cancer, kidney cancer (renal-cell carcinoma), and cancer of the gastrointestinal

tract (MedlinePlus 2009). It is also used to control pleural, peritoneal, and pericardial effusions caused by metastatic tumors. Clinical investigations were performed to evaluate its use in treatment of a variety of nonmalignant diseases, including rheumatoid arthritis, and in tissue transplantation. Research was conducted to investigate its use as a chemosterilant and as a cross-linking agent for the manufacture of ion-exchange fibers. Formerly, the pure form of nitrogen mustard was produced as a potential chemical warfare agent; however, it was never used in combat (IARC 1975).

Production

Nitrogen mustard hydrochloride was produced by one U.S. company from 1950 to the mid 1970s; however, only 1.5 kg (3.3 lb) was manufactured and sold in the United States in 1974 (IARC 1975). Neither nitrogen mustard nor its hydrochloride is now manufactured in commercial quantities in the United States or elsewhere; however, nitrogen mustard hydrochloride is available from eight U.S. suppliers (ChemSources 2009). It is registered by the U.S. Food and Drug Administration for use by one pharmaceutical firm in one product (FDA 2009).

Exposure

The primary routes of potential human exposure to nitrogen mustard hydrochloride are injection, inhalation, and dermal contact. Patients may receive nitrogen mustard hydrochloride as a chemotherapeutic agent by intravenous injection. Intravenous injections may be administered as a single total dose of 0.4 mg/kg of body weight or in two or four daily doses of 0.1 to 0.2 mg/kg (IARC 1975). The one pharmaceutical product containing nitrogen mustard hydrochloride currently registered for use in the United States is intended for intravenous administration. In 2010, 312 clinical trials evaluating the use of nitrogen mustard hydrochloride were in progress or recently completed (ClinicalTrials 2010). The use of a topical cream containing nitrogen mustard hydrochloride to treat mycosis fungoides has been studied. The treatment consisted of applying the ointment or solution to the entire skin surface area once a day for several months until the condition improved; subsequent treatments could be reduced to several times per week (MedlinePlus 2009). As of 2009, no topical creams containing nitrogen mustard hydrochloride were approved by the FDA (FDA 2009).

Nitrogen mustard hydrochloride is not known to occur in nature (IARC 1975), and no environmental releases have been reported to the U.S. Environmental Protection Agency's Toxics Release Inventory. Health professionals potentially may be exposed during preparation, administration, or cleanup of the pharmaceutical product. Potential occupational exposure may also occur during the production of nitrogen mustard hydrochloride and the manufacture, formulation, and packaging of nitrogen mustard hydrochloride pharmaceutical products (IARC 1975). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 4,618 workers, including 2,398 women, potentially were exposed to nitrogen mustard hydrochloride (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Nitrogen mustard is a listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb for nitrogen mustard.

Threshold planning quantity (TPQ) = 10 lb for nitrogen mustard.

Resource Conservation and Recovery Act

Nitrogen mustard hydrochloride salt is listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Nitrogen mustard hydrochloride is a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Guidelines**National Institute for Occupational Safety and Health (NIOSH)**

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

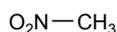
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Nitromethane**CAS No. 75-52-5**

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)

**Carcinogenicity**

Nitromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to nitromethane by inhalation caused tumors in two rodent species and at several different tissue sites. Nitromethane caused benign and malignant mammary-gland tumors (fibroadenoma and carcinoma) in female rats. In mice, it increased the combined incidences of benign and malignant tumors of the Harderian gland (adenoma and carcinoma) and lung (alveolar/bronchiolar adenoma and carcinoma) in both sexes and liver tumors (hepatocellular adenoma and carcinoma) in females (NTP 1997).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to nitromethane.

Studies on Mechanisms of Carcinogenesis

The mechanism by which nitromethane causes cancer is not known. Nitromethane did not cause mutations in bacteria and does not appear to cause genetic damage in mammalian test systems. In cultured mammalian cells, nitromethane did not cause chromosomal aberrations, sister chromatid exchange, or micronucleus formation. Inhalation exposure of mice to nitromethane did not cause micronucleus formation in the erythrocytes, in either bone marrow or peripheral blood (IARC 2000). In cultured Syrian hamster embryo cells, nitromethane induced cell transformation (a step in tumor formation) (Kerckaert *et al.* 1996, NTP 2002). Nitromethane appears to be absorbed by inhalation; the available data suggest that dermal absorption is negligible. Metabolism of nitromethane by experimental animals *in vivo* has not been characterized. Metabolism of nitromethane by rat liver microsomes resulted in formation of only trace amounts of formaldehyde (IARC 2000).

Properties

Nitromethane is a nitroalkane compound that is a colorless oily liquid with a fruity odor at room temperature. It is soluble in water, alcohol, ether, acetone, and dimethylformamide. Nitromethane is sensitive to shock and is unstable when heated. It also forms an explosive sodium salt that bursts into flame on contact with water (Akron, 2009). Physical and chemical properties of nitromethane are listed in the following table (HSDB 2009).

Property	Information
Molecular weight	61.0
Specific gravity	1.1322 at 25°C/4°C
Melting point	-29°C
Boiling point	101.2°C
Log K_{ow}	0.17
Water solubility	111 g/L
Vapor pressure	27.8 mm Hg at 20°C
Vapor density relative to air	2.11
Dissociation constant (pK_a)	10.2 at 25°C

Source: HSDB 2009.

Use

Most of the nitromethane produced in the United States (85% to 90%) is used in the synthesis of nitromethane derivatives used as pharmaceuticals, agricultural soil fumigants, and industrial antimicrobials (Markofsky 1991, Angus 2001). Nitromethane also is used as a fuel or fuel additive with methanol in racing cars, boats, and model engines. It formerly was used in the explosives industry as a component in a binary explosive formulation with ammonium nitrate and in shaped charges, and it was used as a chemical stabilizer to prevent decomposition of various halogenated hydrocarbons (NTP 1997, IARC 2000, Angus 2001).

Production

Nitromethane is produced commercially by high-temperature vapor-phase nitration of propane, a reaction that also yields nitroethane, 1-nitropropane, and 2-nitropropane. In 2001, annual U.S. production was reported to be about 16 million pounds from one producer (Angus 2001). In 2009, nitromethane was available from 16 U.S. suppliers (ChemSources 2009).

Exposure

Nitromethane has been detected in air, surface water, and drinking water (NTP 1997, IARC 2000). The general population may be exposed by inhalation of nitromethane in motor vehicle exhaust and cigarette smoke. In a simulated city driving study, estimated concentrations of nitromethane in motor vehicle exhaust ranged from less than 0.8 to 5.0 ppm, depending on the conditions (Angus 2001). Nitromethane may also be released into air and wastewater during manufacture of royal demolition explosive (RDX) and high melting explosive (HMX), which are widely used in the military. Maximum ground-level concentrations of nitromethane in air at three locations on the boundary of an ammunition plant were 0.21, 2.0, and 2.0 µg/m³ (HSDB 2009, IARC 2000). Nitromethane was identified, but not quantified, as a pollutant in drinking water in two of five cities (Philadelphia, Pennsylvania, and Cincinnati, Ohio) tested in a 1975 U.S. Environmental Protection Agency survey (HSDB 2009). People may also be exposed to nitromethane through skin contact with or accidental ingestion of methanol-nitromethane fuel mixtures. However, products containing nitromethane are not widely used by consumers (IARC 2000).

Occupational exposure to nitromethane may occur through inhalation of vapors or skin contact during its production, use, or disposal. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 134,803 workers, including 46,338 women, potentially were exposed to nitromethane (NIOSH 1990). In addition, workers may have been exposed to nitromethane in the past through exposure to other chemicals (such as 1,1,1-trichloroethane) containing nitromethane as an additive or contaminant (Henschler *et al.* 1980).

Regulations

Department of Transportation (DOT)

Nitromethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture of nitromethane is subject to certain provisions for the control of volatile organic compound emissions.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 100 ppm (250 mg/m³).

Considered a highly hazardous chemical: Threshold quantity (TQ) = 2,500 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 20 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 750 ppm.

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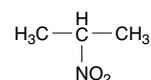
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2-Nitropropane

CAS No. 79-46-9

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

2-Nitropropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Inhalation exposure to 2-nitropropane caused liver tumors (hepatocellular carcinoma) in male rats in two different studies (IARC 1982). Since 2-nitropropane was listed in the *Fourth Annual Report on Carcinogens*, an additional study in rats has been identified. In male rats administered 2-nitropropane by stomach tube for 16 weeks and held for an additional 61 weeks, the incidence of liver cancer was significantly increased (IARC 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to 2-nitropropane.

Properties

2-Nitropropane is a nitroalkane compound which at room temperature is a colorless liquid with a pleasant fruity odor. It is soluble in water and chloroform and miscible with most aromatic hydrocarbons, esters, ethers, ketones, and low-molecular-weight carboxylic acids (HSDB 2009). It is stable under normal temperatures and pressures, but moderately flammable (Akron 2009). Physical and chemical properties of 2-nitropropane are listed in the following table.

Property	Information
Molecular weight	89.1 ^a
Specific gravity	0.9821 at 25°C/4°C ^a
Melting point	-93°C ^a
Boiling point	120.3°C ^a
Log K _{ow}	0.93 ^b
Water solubility	17 g/L at 25°C ^a
Vapor pressure	17.2 mm Hg at 25°C ^a
Vapor density relative to air	3.06 ^a
Dissociation constant (pK _a)	7.68 at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

2-Nitropropane is used principally as a solvent and chemical intermediate (IARC 1982, 1999, HSDB 2009). As a solvent, it is used in

inks, paints, adhesives, varnishes, polymers, and synthetic materials. It is used as a solvent or cosolvent with many resins, and these solvent-resin mixtures are used as coatings, including coatings for beverage cans. 2-Nitropropane is a feedstock for the manufacture of 2-nitro-2-methyl-1-propanol and 2-amino-2-methyl-1-propanol. It is also used as a component of explosives and rocket propellants and as an additive in fuels for internal combustion engines for hobbyists and for racing cars.

Production

U.S. production of 2-nitropropane was estimated at 30 million pounds in 1977 and over 5,000 lb in 1982 (HSDB 2009). One U.S. producer was identified in 1982, and two producers in 1999, but production volumes were not reported (IARC 1982, 1999). In 2009, 2-nitropropane was produced commercially by one manufacturer each in the United States and Europe (SRI 2009) and was available from 16 suppliers, including 8 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule between 1986 and 2002 indicated that U.S. production plus imports of 2-nitropropane total 10 million to 50 million pounds (EPA 2004).

Exposure

The routes of potential human exposure to 2-nitropropane are inhalation, ingestion, and dermal contact (IPCS 1992). For the general population, daily intake of 2-nitropropane has been estimated at 50 to 100 mg, which includes exposure due to its use as a solvent for beverage-can coatings, film-laminating adhesives, and printing inks for food packaging (3 ng) and from vegetable oils (30 ng). Cigarette smokers receive an additional exposure of 1.2 µg per cigarette. 2-Nitropropane was measured in mainstream smoke at concentrations ranging from 19.1 ng per untreated cigarette to 7.4 ng per cigarette for cigarettes with high levels of potassium sorbate (added as a mold inhibitor) (Gaworski *et al.* 2008). 2-Nitropropane was measured in the exhaled breath of healthy nonsmoking urban dwellers at an average concentration of 0.406 ng/L among individuals who had avoided known sources of 2-nitropropane (e.g., medication, perfume, paint, glue, aerosols, dust, tobacco smoke, and areas with polluted air from industrial wastes) for the week prior to sampling and for the duration of sampling (IPCS 1992).

EPA's Toxics Release Inventory reported environmental releases of 2-nitropropane totaling over 655,000 lb in 1988; releases then steadily declined to a low of 16,000 lb in 2003 and were variable through 2007. Half of the releases reported since 1988 have been to air, except in 1989, when a large quantity of 2-nitropropane was released to an underground injection well. In 2007, eight facilities released a total of 28,600 lb of 2-nitropropane (TRI 2009). When released to air, 2-nitropropane photodegrades, with a half-life of 9.8 days, or reacts with hydroxyl radicals, with a half-life of 44 days (HSDB 2009). When released to soil or water, it will volatilize and is not likely to bioaccumulate. However, the portion that does not volatilize from soil may leach into groundwater.

Potential occupational exposure to 2-nitropropane occurs during its manufacture, formulation, and use in industrial construction and maintenance, printing, highway maintenance, and food packaging (IARC 1982). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 29,842 workers potentially were exposed to 2-nitropropane (NIOSH 1976). Subsequent estimates published by the National Institute for Occupational Safety and Health were 100,000 workers in 1977 and 185,000 workers in 1980 (NIOSH 1977, 1980). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,818 workers, including 1,817

women, potentially were exposed to 2-nitropropane (NIOSH 1990). Air concentrations of up to 6,000 mg/m³ have been measured in workplaces. In 1962, monitored concentrations in the air during drum-filling operations ranged from 580 to 1,640 ppm. Of samples taken at a production plant in 1977, 98% had concentrations below the American Conference of Governmental Industrial Hygienists time-weighted-average limit of 10 ppm (IPCS 1992). Average air concentrations were reported to be 0.05 ppm at a tire manufacturing plant and 1 ppm at a chemical plant (IARC 1982). Air concentrations measured in work areas from 1981 to 1983 ranged from 20 to 80 ppm under normal operating conditions. However, the concentrations in all but two personal monitoring samples were at or below 20 ppm; the two highest concentrations were 53 and 73 ppm (Crawford *et al.* 1985).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 2-nitropropane on ships and barges.

Department of Transportation (DOT)

Nitropropanes are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 2-Nitropropane is listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 2-nitropropane = U171, F005.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 25 ppm (90 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 100 ppm.

Listed as a potential occupational carcinogen.

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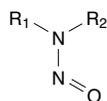
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N-Nitrosamines: 15 Listings



Generic *N*-nitrosamine structure

N-Nitrosamines are a class of chemical compounds with the general structure shown above. The essential feature of *N*-nitroso compounds is the N–N=O structure; the R₁ and R₂ groups attached to the amine nitrogen may range from a simple hydrogen (H) atom to more complex chemical substituents (including ring structures that incorporate the nitrogen atom), as shown in the structures of the individual nitrosamines listed below.

Human exposure to nitrosamines can result from formation of *N*-nitroso compounds either in food during storage or preparation or *in vivo*, usually in the stomach (Mirvish 1975). Individual nitrosamines are not found in isolation, but occur in mixtures of various nitrosamines. Nitrosamines or their precursors occur in a wide variety of foods and manufactured and natural products, such as agricultural chemicals, tobacco, detergents, rust inhibitors, cutting fluids, rubber additives, solvents, drugs, plastics, tanned leather products, textiles, and cosmetics (ATSDR 1989). Nitrosamines generally are not intentionally added to foods or consumer products, but are formed from constituents of the foods or products that are either naturally present, such as the amines that are part of the structure of proteins in meat, or added during production (e.g., nitrates or nitrites added to meats as preservatives). Nitrosamines are formed when nitrites, which can be formed from nitrates, react with a secondary or tertiary amine. The concentration of nitrosamines tends to increase over time, and their formation is enhanced by high temperatures, such as occur while frying food, and high acidity, such as in stomach acid. Ascorbic acid or its isomers inhibit the formation of nitrosamines and often are added to food preparations to prevent nitrosamine formation.

Although food and tobacco products are important sources of external exposure to *N*-nitrosamines, exposure also occurs from nitrosamines produced internally in the digestive tract (Hotchkiss 1989). About 5% of ingested nitrates are reduced to nitrites in saliva (NRC 1995). These nitrites can subsequently react in solution with secondary and tertiary amines, as well as *N*-substituted amides, carbamates, and other related compounds, to form *N*-nitroso compounds within the gastrointestinal tract (Mirvish 1975, Hotchkiss 1989). This internal formation is a major source of human exposure to *N*-nitrosamines.

The listings below are for the individual *N*-nitrosamines and do not constitute a listing for *N*-nitrosamines compounds as a class.

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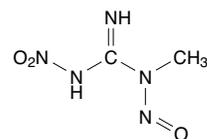
N-Methyl-N'-Nitro-N-Nitrosoguanidine

CAS No. 70-25-7

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as MNNG or 1-methyl-3-nitro-1-nitrosoguanidine



Carcinogenicity

N-Methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

MNNG caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It caused tumors primarily at the site of administration, mostly in the gastrointestinal tract, including tumors of the forestomach (papilloma or carcinoma), glandular stomach (adenoma, adenocarcinoma, carcinoma, or sarcoma), small intestine (papilloma, carcinoma, adenocarcinoma, or sarcoma), and large intestine (adenomatous polyps or polypoid carcinoma). Tumors of the forestomach or glandular stomach were observed in rats exposed to MNNG in the drinking water, by stomach tube, and by intraperitoneal injection; in mice exposed by stomach tube; and in male hamsters and dogs exposed via the drinking water. MNNG also caused tumors of the large intestine in rats exposed by intrarectal instillation. It caused tumors of the small intestine in rats exposed via the drinking water, subcutaneous injection, or intraperitoneal injection and in mice exposed by intraperitoneal injection (IARC 1974, 1987).

In addition, MNNG caused tumors of the liver and peritoneum in rats exposed orally (by stomach tube or drinking water) and injection-site tumors (fibrosarcoma and rhabdomyosarcoma) in rats exposed by subcutaneous injection. In mice, MNNG administered by subcutaneous injection caused benign tumors of the liver, lung, and blood vessels (hemangoendothelioma) and by dermal application caused benign and malignant skin tumors (papilloma and carcinoma) (IARC 1974, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to MNNG. Three deaths from brain tumors (glioma) and one death from colon cancer were reported among workers in a genetics laboratory over a 13-year period. All of the subjects had probably been exposed to MNNG for 6 to 15 years prior to death, but other carcinogens had also been used in the laboratory (IARC 1974, 1987).

Properties

MNNG is an *N*-nitrosamine alkylating agent that exists as a yellow crystal at room temperature and is soluble in water, dimethyl sulfoxide, and polar organic solvents. It reacts violently with water and can explode on heating or high impact. MNNG reacts with various nucleophiles, especially amines (Akron 2009, HSDB 2009). At low pH, it slowly releases nitrous acid, and at high pH in the presence of hydroxyl alkali, it produces the highly toxic gas diazomethane. When MNNG is heated to decomposition, it emits highly toxic fumes of nitrogen oxides (IARC 1974, HSDB 2009). Physical and chemical properties of MNNG are listed in the following table.

Property	Information
Molecular weight	147.1 ^a
Melting point	118°C to 123.5°C (with decomposition) ^a
Log <i>K</i> _{ow}	-0.92 ^b
Water solubility	267 g/L at 25°C ^b
Vapor pressure	0.00012 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

In the 1940s and 1950s, MNNG was used to prepare diazomethane. It currently is used as a research chemical and has no known commercial use (IARC 1974, HSDB 2009).

Production

MNNG is not produced commercially. In 2009, it was available in small quantities for research purposes from seven suppliers worldwide, including five U.S. suppliers (ChemSources 2009).

Exposure

The extent of exposure to MNNG is unknown, but it is probably limited to scientists using it as a research chemical (IARC 1974, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 523 workers potentially were exposed to MNNG (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of MNNG = U163.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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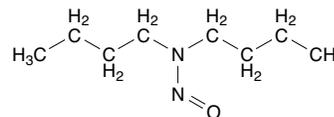
N-Nitrosodi-n-butylamine

CAS No. 924-16-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-dibutylnitrosamine



Carcinogenicity

N-Nitrosodi-*n*-butylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodi-*n*-butylamine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic after a single dose, and was particularly effective as a urinary-bladder carcinogen, causing benign and/or malignant urinary-bladder tumors (papilloma or squamous- or transitional-cell carcinoma) in mice, rats, hamsters, and guinea pigs exposed orally and in mice, rats, hamsters, and rabbits exposed by subcutaneous injection (IARC 1974, 1978).

N-Nitrosodi-*n*-butylamine also caused tumors of the respiratory tract following oral or prenatal exposure in hamsters; subcutaneous injection in rats, hamsters, and adult and newborn mice; and intraperitoneal injection in hamsters of both sexes. Benign or malignant liver tumors were observed in mice, rats, and guinea pigs exposed orally and in newborn mice exposed by subcutaneous injection. Tumors of the upper digestive tract (pharynx, esophagus, or forestomach) occurred following oral exposure in mice, rats, and hamsters and subcutaneous injection in rats (esophagus) and hamsters (forestomach). Intravenous injection of *N*-nitrosodi-*n*-butylamine caused leukemia in mice of both sexes (IARC 1974, 1978).

Since *N*-nitrosodi-*n*-butylamine was listed in the *Second Annual Report on Carcinogens*, an additional study in rats has been identified. Administration of *N*-nitrosodi-*n*-butylamine to male rats by stomach tube caused cancer of the forestomach (carcinoma), in addition to cancer of the liver (carcinoma) and urinary bladder (transitional-cell carcinoma) (Lijinsky and Reuber 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodi-*n*-butylamine.

Properties

N-Nitrosodi-*n*-butylamine is a nitrosamine compound that is a yellow oil at room temperature (HSDB 2009). It is slightly soluble in water and soluble in vegetable oils and organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosodi-*n*-butylamine are listed in the following table.

Property	Information
Molecular weight	158.2 ^a
Specific gravity	0.9009 at 20°C/4°C ^a
Melting point	< 25°C ^b
Boiling point	116°C at 14 mm Hg ^a
Log <i>K</i> _{ow}	2.63 ^a
Water solubility	1.27 g/L at 24°C ^b
Vapor pressure	0.05 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosodi-*n*-butylamine is used primarily as a research chemical (IARC 1974). It has also been used as an intermediate in the synthesis of di-*n*-butylhydrazine.

Production

N-Nitrosodi-*n*-butylamine is not produced commercially in the United States (HSDB 2009). In 2009, it was available in small quantities for research purposes from seven U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosodi-*n*-butylamine are ingestion, inhalation, and dermal contact (HSDB 2009). *N*-Nitrosodi-*n*-butylamine has been detected in a variety of products as a result of the nitrosation of amines present in these products. *N*-Nitrosodi-*n*-butylamine may be formed from secondary or tertiary *n*-butylamines and quaternary ammonium salts by reaction with nitrosating agents, such as nitrite, in the stomach or during cooking processes. The degree of this potential exposure is unknown. *N*-Nitrosodi-*n*-butylamine has been measured in soybean oil at a concentration of 290 µg/kg, in cheese at 20 to 30 µg/kg, and in smoked or cured meats at up to 3.9 µg/kg. It has also been detected in tobacco smoke at a concentration of 3 ng per cigarette. *N*-Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product. Potential exposure depends on the ability of the nitrosamine to migrate from the product into the body. Nitrosamines present in pacifiers and baby-bottle nipples can migrate into saliva, which could result in ingestion of nitrosamines (IARC 1974, 1978).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, all environmental releases of *N*-nitrosodi-*n*-butylamine since 1998 have been to landfills. Annual releases did not exceed 15 lb from 1998 through 2000 or in 2004, but were 4,510 lb in 2001. In 2007, one facility released 500 lb of *N*-nitrosodi-*n*-butylamine to an off-site hazardous-waste landfill (TRI 2009). The estimated half-life of *N*-nitrosodi-*n*-butylamine in the vapor phase is 2.8 days. *N*-Nitrosodi-*n*-butylamine was detected in the effluent water from a coke facility at a concentration of 0.82 µg/L (IARC 1978).

Occupational exposure potentially could occur among researchers studying the biological effects of *N*-nitrosodi-*n*-butylamine.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0063 µg/L; based on fish or shellfish consumption only = 0.22 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which listing is based wholly or partly on the presence of *N*-nitrosodi-*n*-butylamine = U172.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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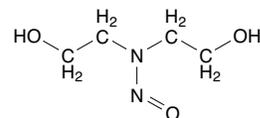
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N-Nitrosodiethanolamine

CAS No. 1116-54-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosodiethanolamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodiethanolamine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Administration of *N*-nitrosodiethanolamine in the drinking water caused liver cancer (hepatocellular carcinoma) and benign kidney tumors (adenoma) in rats of unspecified sex (IARC 1978). Subcutaneous injection of *N*-nitrosodiethanolamine caused cancer of the nasal cavity (adenocarcinoma) and at the injection site (fibrosarcoma) and benign tumors of the trachea (papilloma) and liver (hepatocellular adenoma) in hamsters of both sexes.

Since *N*-nitrosodiethanolamine was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Studies in several strains of rats consistently reported that exposure to *N*-nitrosodiethanolamine in the drinking water caused liver cancer (primarily hepatocellular carcinoma, but also cholangiocellular carcinoma) in both sexes; some studies also found increased incidences of nasal-cavity cancer (adenocarcinoma and squamous-cell carcinoma). In female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), administration of *N*-nitrosodiethanolamine in the drinking water increased the incidence of benign lung tumors and the number of tumors per animal. Tumors of the nasal cavity were observed in hamsters of both sexes exposed to *N*-nitrosodiethanolamine in several studies by subcutaneous injection and in one study by swabbing of the oral cavity (IARC 2000).

Cancer Studies in Humans

No epidemiological studies evaluating the relationship between human cancer and exposure specifically to *N*-nitrosodiethanolamine were available when it was listed in the *Second Annual Report on Carcinogens*. Since then, the International Agency for Research on Cancer (IARC 2000) concluded that there was inadequate evidence of the carcinogenicity of *N*-nitrosodiethanolamine from studies in humans. *N*-Nitrosodiethanolamine can be formed from ethanolamines and sodium nitrates, which are additives to soluble and synthetic metalworking fluids. In a review of studies of workers exposed to metalworking fluids, IARC noted increased cancer mortality or incidence among workers using fluids containing ethanolamines and sodium nitrates. One study found that esophageal cancer increased with increasing duration of exposure to nitrosamines as assessed by coexposure to ethanolamines and sodium nitrate; however, the same workers were also exposed to biocides.

Properties

N-Nitrosodiethanolamine is a nitrosamine compound that exists at room temperature as a yellow oil with no distinctive odor (HSDB 2009). It is miscible in water and soluble in polar organic solvents, but insoluble in nonpolar organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978, Akron 2009). Physical and chemical properties of *N*-nitrosodiethanolamine are listed in the following table.

Property	Information
Molecular weight	134.1 ^a
Boiling point	114°C at 1.4 mm Hg ^a
Log <i>K</i> _{ow}	-1.28 ^b
Water solubility	1,000 g/L ^b
Vapor pressure	0.0005 mm Hg at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosodiethanolamine is used primarily as a research chemical and has no known commercial uses (HSDB 2009).

Production

N-Nitrosodiethanolamine is not produced commercially in the United States (HSDB 2009). In 2009, it was available in small quantities for research purposes from 11 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosodiethanolamine are dermal contact, ingestion, and inhalation (HSDB 2009). *N*-Nitrosodiethanolamine is widespread in the environment. It is a known contaminant of cosmetics, lotions, shampoos, cutting fluids, certain pesticides, antifreeze, and tobacco at concentrations of up to 130 ppm (130,000 ppb) (IARC 2000). Nitrosamines are formed within these products by reactions of precursors (nitrosating agents and primary or secondary amines) or are introduced through the use of contaminated raw materials (Schothorst and Somers 2005).

As of 1980, the U.S. Food and Drug Administration had analyzed over 300 cosmetic products and found that over 40% were contaminated with *N*-nitrosodiethanolamine. It was detected in facial cosmetics at concentrations of 42 to 49,000 µg/kg, in lotions at up to 140 µg/kg, and in shampoos at up to 260 mg/kg (IARC 1978). Cosmetics at least five years old had higher concentrations of *N*-nitrosodiethanolamine than new samples of the same products, indicating that the formation of *N*-nitrosodiethanolamine limits the shelf-life of cosmetic products (Matyska *et al.* 2000). *N*-Nitrosodiethanolamine was also measured in 35 of 140 soap and shampoo products at concentrations of 23 to 992 µg/kg (Schothorst and Somers 2005). *N*-Nitrosodiethanolamine was detected in cigarette smoke at concentrations of 24 to 36 ng per cigarette and in smokeless tobacco products at up to 6.8 µg/g (Brunnemann and Hoffmann 1981, Brunnemann *et al.* 1982). The presence of *N*-nitrosodiethanolamine in tobacco is attributed to the use of an herbicide, maleic hydrazide diethanolamine, commonly applied to tobacco (IARC 2000).

Occupational exposure to *N*-nitrosodiethanolamine could occur during the use of synthetic cutting fluids to reduce the temperature of the metal-tool interface during metal cutting or grinding. *N*-Nitrosodiethanolamine is present in most cutting fluids containing triethanolamine and sodium nitrite, at concentrations ranging from 0.02% to 3% (IARC 1978). In addition, an atrazine pesticide formulation emulsified with triethanolamine was reported to contain *N*-nitrosodiethanolamine at a concentration of 0.5 mg/kg (IARC 1978). In 1976, the National Institute for Occupational Safety and Health estimated that 780,000 workers potentially were exposed to cutting fluids during their manufacture and use (NIOSH 1976). In a study of factory workers directly exposed to metalworking fluids, the post-shift concentration of *N*-nitrosodiethanolamine in the urine of workers using the cutting fluids was highly correlated with the concentration of *N*-nitrosodiethanolamine in the cutting fluids; urinary concentrations were up to 277 µg/L in workers using "nitrate-formulated" fluids, compared with 2.7 µg/L in workers using "nitrate-free" fluids. When nitrite concentrations in cutting fluids were less than 20 mg/L, *N*-nitrosodiethanolamine levels in the fluids remained below 5 mg/L (Ducos *et al.* 1999, Ducos and Gaudin 2003).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of N-nitrosodiethanolamine = U173.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for N-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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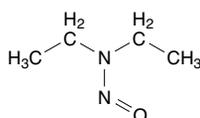
N-Nitrosodiethylamine

CAS No. 55-18-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as diethylnitrosamine



Carcinogenicity

N-Nitrosodiethylamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodiethylamine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally and as adults, causing tumors mainly in the liver, respiratory tract, kidney, and upper digestive tract (IARC 1972, 1978).

Benign and malignant liver tumors occurred in mice, rats, hamsters, guinea pigs, rabbits, dogs, and pigs orally exposed to N-nitrosodiethylamine. Liver tumors also occurred in rats following inhalation exposure or rectal administration; in mice, rats, and hamsters following intraperitoneal injection; in hamsters, guinea pigs, gerbils, and hedgehogs following subcutaneous injection; in mice following prenatal exposure; in birds following intramuscular injection; and in fish and frogs exposed to N-nitrosodiethylamine in the tank water. In dogs, exposure to N-nitrosodiethylamine by stomach tube followed by subcutaneous injection caused cancer of the liver and nasal cavity (squamous-cell carcinoma).

Tumors of the lung and upper respiratory tract occurred in mice, rats, hamsters, dogs, and pigs following oral administration of N-nitrosodiethylamine. Inhalation exposure caused tumors of the trachea, bronchi, and lungs in hamsters, and dermal exposure caused tumors of the nasal cavity in mice and hamsters. Subcutaneous injection caused respiratory-tract tumors in adult and newborn mice and hamsters, in pregnant hamsters (benign tracheal tumors), and in adult guinea pigs, gerbils, and hedgehogs. Intraperitoneal injection caused lung tumors in mice and respiratory-tract tumors in hamsters and monkeys, and intravenous injection caused tumors of the nasal cavity in gerbils. Prenatal exposure caused benign lung tumors (adenoma) in mice and hamsters.

Tumors of the kidney occurred in rats following oral, intravenous, or prenatal administration of N-nitrosodiethylamine. Oral administration also caused kidney tumors in pigs and tumors of the upper digestive tract in mice, rats, and hamsters. Prenatal exposure caused benign and malignant tumors of the upper digestive tract in mice and tumors of the thymus (thymoma) and benign mammary-gland tumors (adenoma) in rats. One study reported hematopoietic-system tumors in frogs exposed to N-nitrosodiethylamine in the tank water.

Since N-nitrosodiethylamine was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. As in earlier studies, the most common tumor sites were the liver, kidney, digestive tract, and respiratory tract. However, some of these studies reported that N-nitrosodiethylamine caused tumors by additional routes of exposure, in additional species, or at additional tissue sites. Liver tumors were also observed in (1) chickens after intramuscular administration, (2) cats after oral administration (dietary or by stomach tube) (Schmahl *et al.* 1978), and (3) newborn mice after intraperitoneal injection (Lai and Arcos 1980, Vesselinovitich *et al.* 1984). Tumors of the lung or trachea were also observed in (1) hamsters of both sexes after intratracheal administration (Yamamoto *et al.* 1985, Ishinishi *et al.* 1988, Tanaka *et al.* 1988), (2) rabbits after subcutaneous injection (Huntrakoon *et al.* 1989), (3) newborn mice after intraperitoneal injection (Vesselinovitich *et al.* 1984), and (4) snakes after oral exposure (Schmahl and Scherf 1983, 1984). Kidney tumors also were observed in orally exposed snakes. Addition of N-nitrosodiethylamine to the tank water increased the incidence of benign or malignant pancreatic tumors (adenoma, cystadenoma, or adenocarcinoma) in larval or juvenile fish (Thiyagarajah and Grizzle 1986) and tumors of the digestive gland and hematopoietic system in mollusks (Khudoley and Syrenko 1978). Benign laryngotracheal tumors (papilloma) were observed in pregnant hamsters exposed by intraperitoneal injection and in the prenatally exposed offspring, and

laryngotracheal tumors (neuroendocrine-cell tumors) were observed in the second generation of offspring (Mohr *et al.* 1995).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodiethylamine.

Properties

N-Nitrosodiethylamine is a nitrosamine compound that is a slightly yellow, volatile liquid at room temperature (HSDB 2009). It is soluble in water, ethanol, ether, organic solvents, and lipids. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light. (IARC 1978). Physical and chemical properties of *N*-nitrosodiethylamine are listed in the following table.

Property	Information
Molecular weight	102.1 ^a
Specific gravity	0.9422 at 20°C/4°C ^a
Melting point	< 25°C ^b
Boiling point	175°C to 177°C ^a
Log <i>K</i> _{ow}	0.48 ^a
Water solubility	106 g/L at 24°C ^b
Vapor pressure	0.86 mm Hg at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosodiethylamine is used primarily as a research chemical (HSDB 2009). Previously, it was used as a gasoline and lubricant additive, antioxidant, stabilizer in plastics, fiber-industry solvent, and copolymer softener, and in the synthesis of 1,1-diethylhydrazine. It was also used to increase dielectric constants in condensers (IARC 1972, HSDB 2009).

Production

No commercial producers of *N*-nitrosodiethylamine were identified. In 2009, it was available from 11 U.S. suppliers (ChemSources 2009). No data on U.S. production, imports, or exports of *N*-nitrosodiethylamine were found.

Exposure

The routes of potential human exposure to *N*-nitrosodiethylamine are ingestion, inhalation, and dermal contact. The general population may be exposed to unknown quantities of *N*-nitrosodiethylamine present in foods, beverages, tobacco smoke, drinking water, and industrial pollution (HSDB 2009). Intake from exposure via air, diet, and smoking has been estimated at a few micrograms per day. *N*-Nitrosodiethylamine has been measured in a variety of foods, including cheese at concentrations of 0.5 to 30 µg/kg, soybeans at 0.2 µg/kg, soybean oil at 4 µg/kg, various fish at up to 147 µg/kg, salt-dried fish at 1.2 to 21 mg/kg, cured meats at up to 40 µg/kg, and alcoholic beverages at 0.1 µg/kg. *N*-Nitrosodiethylamine was detected in tobacco-smoke condensate at concentrations of 1.0 to 28 ng per cigarette (IARC 1978). Up to 8.3 ng per cigarette was found in mainstream smoke and 8 to 73 ng in sidestream smoke. *N*-Nitrosodiethylamine was found at concentrations of up to 0.2 ng/L in indoor air polluted with tobacco smoke and at 10 ng/m³ in the smoking compartment of a train (Brunnemann *et al.* 1977, Brunnemann and Hoffmann 1978).

Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product (HSDB 2009). Potential exposure depends on the ability of the nitrosamines to migrate from the product into the body. Nitrosamines

present in pacifiers and baby-bottle nipples can migrate into saliva, which could result in ingestion of nitrosamines (IARC 1974, 1978).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 11,795 lb of waste containing *N*-nitrosodiethylamine was released by three facilities in 1999; 99.6% was released to land. In 2007, one facility released 500 lb of *N*-nitrosodiethylamine to a hazardous-waste landfill (TRI 2009). *N*-Nitrosodiethylamine is widespread in the environment, but is rapidly decomposed by sunlight and does not usually persist in ambient air or water exposed to sunlight. It was found at concentrations of 0.07 and 0.24 µg/L in wastewater from two chemical plants, 0.010 µg/L in high-nitrate well water for drinking, and 0.33 to 0.83 µg/L in deionized water (HSDB 2009). *N*-Nitrosodiethylamine and other nitrosamines were found at very low concentrations in ion-exchange resins (Gough *et al.* 1977).

There is some potential for occupational exposure of laboratory, copolymer, and lubricant workers to *N*-nitrosodiethylamine (IARC 1972, 1978). No data were found on the numbers of workers potentially exposed.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L; based on fish or shellfish consumption only = 1.24 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodiethylamine = U174.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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Properties

N-Nitrosodimethylamine is a nitrosamine compound that exists at room temperature as a yellow liquid with a faint characteristic odor (Akron 2009). It is very soluble in water, alcohol, and ether, miscible with methylene chloride and vegetable oils, and soluble in lipids, chloroform, and most other organic solvents (HSDB 2009). It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosodimethylamine are listed in the following table.

Property	Information
Molecular weight	74.1 ^a
Specific gravity	1.0048 at 20°C/4°C ^a
Melting point	< 25°C ^b
Boiling point	151°C to 153°C ^a
Log <i>K</i> _{ow}	-0.57 ^a
Water solubility	1,000 g/L at 24°C ^b
Vapor pressure	2.7 mm Hg at 20°C ^b
Vapor density relative to air	2.56 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosodimethylamine is used primarily as a research chemical (HSDB 2009). Before April 1, 1976, it was used as an intermediate in the electrolytic production of 1,1-dimethylhydrazine, a storable liquid rocket fuel containing approximately 0.1% *N*-nitrosodimethylamine as an impurity (IARC 1978). Other former uses of *N*-nitrosodimethylamine include use in control of nematodes, to inhibit nitrification in soil, in active metal anode-electrolyte systems (high-energy batteries), in the preparation of thiocarbonyl fluoride polymers, and as a plasticizer for rubber and acrylonitrile polymers, a solvent in the fiber and plastics industry, an antioxidant, a softener of copolymers, and an additive to lubricants (HSDB 2009).

Production

Commercial production of *N*-nitrosodimethylamine in the United States began in the mid 1950s for use in the manufacture of 1,1-dimethylhydrazine. The last commercial producer of *N*-nitrosodimethylamine closed its plant in 1976 (IARC 1978), and there is no evidence that *N*-nitrosodimethylamine is currently manufactured commercially in the United States (HSDB 2009). In 2009, *N*-nitrosodimethylamine was available from nine U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of *N*-nitrosodimethylamine were found.

Exposure

The routes of potential human exposure to *N*-nitrosodimethylamine are ingestion, inhalation, and dermal contact (HSDB 2009). The general population may be exposed to unknown quantities of *N*-nitrosodimethylamine present in foods and beverages, tobacco smoke, herbicides, pesticides, drinking water, and industrial pollution (IARC 1978, ATSDR 1989). In addition, nitrosamines may be formed from amines reacting with nitrites in the human body as a result of ingestion of these precursors separately in food, water, or air. Intake of *N*-nitrosodimethylamine from exposure via air, diet, and smoking has been estimated at a few micrograms per day. *N*-Nitrosodimethylamine is present in a variety of foods, including cheese, soybean oil, various meat products, bacon, various cured meats, frankfurters, cooked ham, fish and fish products, spices used for meat curing, apple brandy, other alcoholic beverages, and beer. Concentrations in

these foodstuffs have been measured at up to 850 µg/kg (in spices used in curing) (IARC 1978).

N-Nitrosodimethylamine has been detected in numerous drugs formulated with aminopyrene, including tablets, suppositories, injections, drops, and syrups, at concentrations ranging from less than 10 to 371 µg/kg. *N*-Nitrosodimethylamine was measured in mainstream cigarette smoke at 13 to 65 ng per cigarette for nonfiltered cigarettes and 5.7 to 43 ng for filtered cigarettes and in sidestream smoke at 680 to 823 ng for nonfiltered cigarettes and 1,040 to 1,770 ng for filtered cigarettes. It was found at concentrations of 90 to 240 ng/m³ in smoke-filled rooms, such as bars, but at less than 5 ng/m³ in residences (IARC 1978). Nitrosamines frequently are produced during rubber processing and may be present as contaminants in the final rubber product. Potential exposure depends on the ability of the nitrosamine to migrate from the product into the body. Dimethylamine-formulated pesticides and herbicides contained *N*-nitrosodimethylamine at 190 to 640 mg/L (190,000 to 640,000 µg/L) (ATSDR 1989).

N-Nitrosodimethylamine is widespread in the environment, but it is rapidly decomposed by sunlight and does not usually persist in ambient air or water exposed to sunlight (ATSDR 1989). *N*-Nitrosodimethylamine was found at concentrations of 0.25 µg/L in industrial wastewater from chemical factories, 0.02 to 0.82 µg/L in chlorinated drinking water, less than 0.01 µg/L in high-nitrate well water, and 0.012 to 0.34 µg/L in deionized water. *N*-Nitrosodimethylamine and other nitrosamines were found at very low concentrations in ion-exchange resins (Gough *et al.* 1977). Soil samples taken near industrial plants contained *N*-nitrosodimethylamine at concentrations of up to 15.1 ng/g (IARC 1978).

There is some potential for occupational exposure of laboratory, copolymer, lubricant, and pesticide workers to *N*-nitrosodimethylamine (IARC 1978, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 747 workers, including 299 women, potentially were exposed to *N*-nitrosodimethylamine (NIOSH 1990). Occupational Safety and Health Administration regulations concerning *N*-nitrosodimethylamine designate strict procedures to avoid worker contact (IARC 1978). Mixtures containing *N*-nitrosodimethylamine at 1.0% or more must be maintained in isolated or closed systems, workers must observe special hygiene rules, and certain procedures must be followed for movement of the material and in case of accidental spills and emergencies.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00069 µg/L; based on fish or shellfish consumption only = 3.0 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 1,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosodimethylamine = P082.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

Action levels for *N*-nitrosodimethylamine in barley malt and malt beverages range from 5 to 10 ppb. The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb. In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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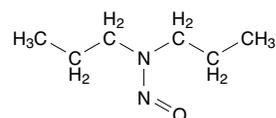
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N-Nitrosodi-*n*-propylamine**CAS No. 621-64-7**

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

**Carcinogenicity**

N-Nitrosodi-*n*-propylamine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosodi-*n*-propylamine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. In rats, it caused liver cancer (hepatocellular carcinoma) and benign and malignant tumors of the esophagus (papilloma and carcinoma) following administration in the drinking water or subcutaneous injection (IARC 1978). Subcutaneous injection of *N*-nitrosodi-*n*-propylamine also caused tumors of the lung and nasal and paranasal cavities in hamsters and rats, tumors of the laryngobronchial tract in hamsters, and benign and malignant kidney tumors (adenoma and adenocarcinoma) in rats.

Since *N*-nitrosodi-*n*-propylamine was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animal have been identified, which reported that *N*-nitrosodi-*n*-propylamine caused tumors of the liver, esophagus, and respiratory tract by additional routes of exposure or in additional species. Liver tumors were observed in monkeys exposed by intraperitoneal injection (Adamson and Sieber 1979, 1982); cancer (carcinoma) of the liver, esophagus, and nasal cavity in rats exposed by stomach tube (Lijinsky and Reuber 1983); and tracheal tumors in male hamsters exposed by intratracheal instillation (Ishinishi *et al.* 1988). In addition, administration of *N*-nitrosodi-*n*-propylamine in the drinking water caused forestomach tumors in male rats (Lijinsky *et al.* 1981).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodi-*n*-propylamine.

Properties

N-Nitrosodi-n-propylamine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is soluble in water, lipids, and organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of N-nitrosodi-n-propylamine are listed in the following table.

Property	Information
Molecular weight	130.2 ^a
Specific gravity	0.9160 at 20°C/4°C ^a
Boiling point	206°C ^b
Log <i>K</i> _{ow}	1.36 ^a
Water solubility	13 g/L at 24°C ^b
Vapor pressure	0.086 mm Hg at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosodi-n-propylamine is used in small quantities in laboratory research. It has no known commercial use (IARC 1978, ATSDR 1989, HSDB 2009).

Production

N-Nitrosodi-n-propylamine was first prepared in 1886, but it has never been produced in commercial quantities (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

The primary routes of potential human exposure to N-nitrosodi-n-propylamine are inhalation, ingestion, and dermal contact (HSDB 2009). N-Nitrosodi-n-propylamine has been detected in extruded rubber products, cheese, and alcoholic beverages, and in the herbicides trifluralin, isopropalin, and oryzalin at low concentrations (17 to 190 ppm) (IARC 1978, ATSDR 1989, HSDB 2009). There is some evidence that N-nitrosodi-n-propylamine may be formed in the upper gastrointestinal tract following ingestion of foods containing nitrites and secondary amines (ATSDR 1989). It may also occur in cigarette smoke at low levels (about 1 ng per cigarette). N-Nitrosodi-n-propylamine is not commonly detected in the environment. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, two facilities released a total of 2,379 lb of N-nitrosodi-n-propylamine to the environment in 1998, and one facility released 5 lb in 1999. Since 2001, releases have ranged from a low of 257 lb in 2002 to a high of 755 lb in 2005. In 2007, 250 lb was released to air and 500 lb to an off-site hazardous-waste landfill (TRI 2009). When released to the environment, N-nitrosodi-n-propylamine will undergo photochemical and biological degradation and will not persist. N-Nitrosodi-n-propylamine has been detected in some samples of wastewater from chemical plants (ATSDR 1989).

Occupational exposure to N-nitrosodi-n-propylamine may occur through inhalation and dermal contact during herbicide application (HSDB 2009) or production of extruded rubber parts (ATSDR 1989). N-Nitrosodi-n-propylamine was not detected in air samples collected at agricultural fields before, during, or after application of trifluralin. However, at an automobile plant where workers were involved in the production of extruded rubber parts, it was found in air samples at concentrations of 1.3 to 3.3 µg/m³. In the vulcanization step of tire manufacturing, N-Nitrosodi-n-propylamine was measured at concentrations of up to 1.086 mg/m³, resulting in an estimated daily intake of 0.0029 mg/kg of body weight for workers (Durmusoglu 2007). No

data were available on the numbers of workers potentially exposed to N-nitrosodi-n-propylamine.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0050 µg/L; based on fish or shellfish consumption only = 0.51 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of N-nitrosodi-n-propylamine = U111.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for N-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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- TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select N-Nitrosodi-n-Propylamine.

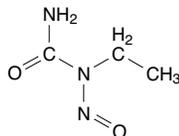
N-Nitroso-N-ethylurea

CAS No. 759-73-9

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-ethyl-*N*-nitrosourea



Carcinogenicity

N-Nitroso-*N*-ethylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitroso-*N*-ethylurea caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally and as adults. Perinatal exposure caused primarily nervous-system tumors, whereas tumors occurred at numerous tissue sites in adults, including the kidney and lymphoreticular system.

Tumors of the nervous system (brain, spinal cord, or peripheral nerves) were observed following oral exposure to *N*-nitroso-*N*-ethylurea in suckling rats, a single subcutaneous injection in newborn rats, and prenatal exposure in mice, rats, hamsters, and rabbits. In adult rodents, intraperitoneal injection of *N*-nitroso-*N*-ethylurea caused brain tumors in mice, and intravenous injection caused tumors of the brain and peripheral nerves in rats (IARC 1972, 1978).

Prenatal exposure to *N*-nitroso-*N*-ethylurea also caused benign lung tumors (adenoma), leukemia, and tumors of the liver, Harderian gland, and endocrine glands in mice; benign and malignant kidney tumors (adenoma, adenocarcinoma, and adenocarcinoma) in rabbits; and benign tumors of the sweat glands (adenoma) and skin (papilloma) in pigs. Oral exposure caused leukemia in adult rats, kidney tumors (nephroblastoma) in suckling rats, and tumors of the kidney (nephroblastoma), eye, liver, muscle, and jaw in newborn opossums. Intravenous injection of *N*-nitroso-*N*-ethylurea caused tumors of the kidney, ovary, uterus, and vagina in rats and tumors of the ovary, uterus, bone, skin, and blood vessels in monkeys. Intraperitoneal injection caused thymic lymphoma and myeloid leukemia in rats and lymphoma and tumors of the liver, kidney, ovary, lung, Harderian gland, stomach in mice. In newborn mice, a single subcutaneous injection of *N*-nitroso-*N*-ethylurea caused lymphoma, liver cancer (hepatocellular carcinoma), and benign and malignant lung tumors (adenoma and adenocarcinoma) (IARC 1972, 1978).

Since *N*-nitroso-*N*-ethylurea was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animal have been identified, which confirmed the induction of several tumors types observed in earlier studies and reported that it caused tumors by additional routes of exposure, in additional species, and at additional tissue sites. Tumors were observed for the following additional routes of exposure or additional species:

- Intratracheal administration caused benign tracheal tumors (papilloma and polyps) in male hamsters (Grubbs *et al.* 1981).
- Dermal administration caused skin tumors in mice (Lijinsky 1982, Lijinsky and Reuber 1983).

- Implantation into the mammary gland caused mammary-gland cancer (adenocarcinoma) in female rats (Holtzman *et al.* 1985).
- Intracerebral injection caused brain tumors in adult rats (Druckrey 1973), and a single intracerebral injection caused spinal-cord tumors in newborn rats of both sexes (Pfaffenroth and Das 1979).
- Intravesicular administration caused urinary-bladder tumors in female rats (Lijinsky *et al.* 1992).
- Injection directly into the amniotic sac of pregnant mice caused benign lung tumors (alveogenic adenoma) in the offspring (Rossi *et al.* 1979).
- In fish, exposure in the tank water caused benign skin tumors (papilloma) (Beckwith *et al.* 2000).
- In gerbils, subcutaneous injection caused nervous-system tumors (oligodendroglioma) and skin cancer (melanoma) in newborns of both sexes and benign blood-vessel tumors (hemangioma) in adults of both sexes (Naito *et al.* 1985).

N-nitroso-*N*-ethylurea also caused tumors at the following additional tissue sites:

- Benign forestomach tumors (squamous-cell papilloma) were observed in male hamsters exposed by intraperitoneal injection, as well peripheral-nerve tumors in prenatally exposed hamsters (Likhachey *et al.* 1983, Diwan *et al.* 1996).
- Malignant placental tumors (choriocarcinoma) were observed in pregnant monkeys exposed by intravenous injection (Rice *et al.* 1981).
- Tumors of the lining of the peritoneal cavity (mesothelioma) were observed in orally exposed male rats, as well as mammary-gland tumors in orally exposed female rats (Lijinsky and Kovatch 1989).

Intraperitoneal injection of *N*-nitroso-*N*-ethylurea in rats caused mammary-gland tumors in males, ovarian tumors in females, nervous-system tumors adult males and newborns, and possibly kidney tumors in newborns (Mandybur *et al.* 1978, Stoica and Koestner 1984, Stoica *et al.* 1985, Hasegar *et al.* 1989). Prenatal exposure of mice to *N*-nitroso-*N*-ethylurea caused benign skin tumors (papilloma and sebaceous adenoma) in nude mice and cancer of the small intestine (adenocarcinoma) in mice of both sexes in other mouse strains (Anderson *et al.* 1982, Oomen *et al.* 1984, 1988, 1989). Prenatal exposure of rabbits caused tumors of the kidney and neural tissue (neurofibroma) (Fox *et al.* 1982).

Oral administration of *N*-nitroso-*N*-ethylurea to rats caused thyroid-gland tumors, forestomach cancer (squamous-cell carcinoma), and benign lung tumors (adenoma) in both sexes; tumors of the colon and skin in males; and ovarian tumors (Sertoli-cell tumors) in females (Maekawa *et al.* 1984, Lijinsky *et al.* 1985, Maekawa *et al.* 1986, Lijinsky and Kovatch 1989, 1996). Administration by stomach tube to hamsters caused benign and malignant forestomach tumors (papilloma and squamous-cell carcinoma) and blood-vessel cancer (hemangiosarcoma) in both sexes (Lijinsky *et al.* 1985).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitroso-*N*-ethylurea.

Properties

N-Nitroso-*N*-ethylurea is a nitrosamine compound that exists as yellow-pink or buff-yellow crystals at room temperature (HSDB 2009). It is soluble in water, chloroform, and other polar organic solvents,

but insoluble in non-polar organic solvents. It decomposes in alkaline solution at a rate that depends on pH (IARC 1978). The pure compound is sensitive to moisture and light and should be stored under refrigeration. Physical and chemical properties of *N*-nitroso-*N*-ethylurea are listed in the following table.

Property	Information
Molecular weight	117.1 ^a
Melting point	103°C to 104°C (with decomposition) ^a
Log K_{ow}	0.23 ^a
Water solubility	13 g/L at 25°C ^b
Vapor pressure	0.0183 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitroso-*N*-ethylurea has been used to synthesize diazoethane in the laboratory, and its mutagenic effects have been studied for promoting the growth of various plants (IARC 1978).

Production

N-Nitroso-*N*-ethylurea was first prepared in 1919 but has never been produced in commercial quantities in the United States (IARC 1978). In 2009, it was available in small quantities for research purposes from six U.S. suppliers (ChemSources 2009).

Exposure

The potential for human exposure is limited, because *N*-nitroso-*N*-ethylurea is not produced or used in large quantities in the United States (IARC 1978). Human exposure to *N*-nitroso compounds may occur through absorption from food, water, and air, and from formation in the human body from precursors ingested separately from food or water (IARC 1978). Exposure may also result from the consumption or smoking of tobacco. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of *N*-nitroso-*N*-ethylurea totaled of 169 lb in 1999 and 255 lb in 2001, but only 10 lb in 2005, 2006, and 2007 (TRI 2009). In air, *N*-nitroso-*N*-ethylurea exists solely as vapor and is degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 3.2 days. It hydrolyzes in water, with a half-life of 1.5 hours at pH 7 at 20°C. Occupational exposure to *N*-nitroso-*N*-ethylurea may occur through inhalation or dermal contact during its use in research (HSDB 2009). No data were found on the numbers of workers potentially exposed to *N*-nitroso-*N*-ethylurea.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitroso-*N*-ethylurea = U176.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select *N*-Nitroso-*N*-Ethylurea .

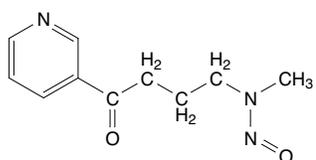
4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone

CAS No. 64091-91-4

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as NNK or 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone



Carcinogenicity

4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

NNK caused tumors in three rodent species and at several different tissue sites, primarily tumors of the lung and nasal cavity in rats and hamsters. In some studies, NNK caused tumors after a single injection, and dose-response relationships were observed for liver, lung, and nasal-cavity tumors in rats. Subcutaneous injection of NNK caused benign or malignant nasal-cavity tumors (squamous- or transitional-cell papilloma, neuroblastoma, rhabdomyosarcoma, esthesioneuroepithelioma, squamous-cell carcinoma, anaplastic carcinoma, or spindle-cell sarcoma) and lung cancer (squamous-cell carcinoma, adenocarcinoma, and adenosquamous-cell carcinoma) in rats and hamsters of both sexes (IARC 1985). Subcutaneous injection of NNK also caused cancer of the liver (hepatocellular carcinoma) and the blood vessels (hemangiosarcoma) in rats of both sexes and tracheal tumors in hamsters of both sexes after single or multiple injections. In female strain A mice (a strain with a high spontaneous incidence of lung tumors), intraperitoneal injection of NNK caused benign and malignant lung tumors (adenoma and carcinoma).

Since NNK was listed in the *Sixth Annual Report on Carcinogens*, additional studies have been identified in which NNK was carcinogenic by additional routes of exposure or in additional species. The majority of these studies confirmed that NNK primarily caused tumors of the lung, nasal cavity, and liver in rodents:

- Oral administration (by stomach tube or in the drinking water) caused lung tumors in strain A/J mice (Chung 1999, Sugimoto *et al.* 2003, Kim *et al.* 2004, Richie *et al.* 2006) and male rats (Rivenson *et al.* 1988, Lijinsky *et al.* 1991a, Hoffmann *et al.* 1993, Hecht *et al.* 1996), nasal-cavity tumors in rats of both sexes, and liver tumors in male rats (Lijinsky *et al.* 1991a).

- Swabbing of the oral cavity with NNK caused tumors of the lung, nasal cavity, and liver in rats (Prokopczyk *et al.* 1991).
- Administration onto the tongue caused lung tumors in mice (Padma *et al.* 1989).
- Intravesicular instillation caused lung and liver tumors in female rats (Lijinsky *et al.* 1991b).
- Intraperitoneal injection caused lung and liver tumors in newborn mice of both sexes (Anderson *et al.* 1991, Beebe *et al.* 1993).
- Prenatal exposure of hamsters caused nasal-cavity tumors (Correa *et al.* 1990, Schuller *et al.* 1994).
- In female mink, subcutaneous injection caused nasal-cavity tumors (Koppang *et al.* 1997).

NNK also was found to cause tumors at additional tissues sites. Prenatal exposure of hamsters caused adrenal-gland tumors in both sexes (Schuller *et al.* 1993, 1994) and caused tumors of the larynx and trachea, in addition to the nasal cavity (Correa *et al.* 1990). Administration of NNK in the drinking water of male rats also increased the combined incidences of leukemia and lymphoma (Hecht *et al.* 1996) and benign and malignant tumors of the pancreas (exocrine acinar adenoma and adenocarcinoma) (Rivenson *et al.* 1988, Hoffmann *et al.* 1993).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to NNK.

Properties

NNK is a tobacco-specific nitrosamine compound. In its pure form, NNK is a pale-yellow crystalline solid at room temperature (Akron 2009). It is soluble in water (SRC 2009). Physical and chemical properties of NNK are listed in the following table.

Property	Information
Molecular weight	207.2 ^a
Melting point	71°C to 73°C ^a
Water solubility	40.5 g/L at 25°C ^b
Dissociation constant (pK _a)	10.57 ^a

Sources: ^aAkron 2009, ^bSRC 2009.

Use

NNK has no known use other than as a laboratory chemical; it has been used as a positive-control substance in laboratory carcinogenicity studies (IARC 1985, 2007).

Production

Synthetic NNK is prepared by reacting sodium hydroxide and sodium nitrite with 4-(*N*-methyl)-1-(3-pyridyl)-1-butanone dihydrochloride or by reacting nicotine with sodium nitrite in aqueous solution. NNK is not produced commercially (IARC 1985). In 2009, it was available in small quantities for research purposes from six suppliers worldwide, including four U.S. suppliers (ChemSources 2009).

Exposure

Potential exposure to NNK is widespread among tobacco-product users and people exposed to sidestream smoke. NNK has been measured in tobacco at concentrations of 0.1 to 35 mg/kg. It was found in moist snuff at up to 18 mg/kg (dry weight), in dry snuff at up to 84.4 mg/kg, in leading U.S. brands of snuff at 0.2 to 8.3 mg/kg, in U.S. chewing tobacco products at up to 1.1 mg/kg (dry weight), in U.S. cigarettes at up to 1.27 mg/kg of dry tobacco (IARC 1985, 2007), and in Nigerian or American cigarettes at 55 to 317 ng per cigarette

(Atawodi *et al.* 1995, Harris 2001). NNK was found in the tobacco of bidi cigarettes at concentrations ranging from 0.10 to 0.85 mg/kg, compared with 0.11 to 0.28 mg/kg for U.S. cigarettes (Wu *et al.* 2004).

NNK has been found in mainstream smoke from U.S. cigarettes at concentrations of up to 425 ng per cigarette (IARC 2007). NNK was measured in cigarette and cigar smoke at 0.9 to 7 mg/kg, in mainstream cigarette at 0.02 to 4.2 µg per cigarette, and in sidestream smoke at 0.2 to 15.7 µg per cigarette (IARC 1985). One study found NNK concentrations to be 45% to 73% lower in smoke from filtered than non-filtered cigarettes. NNK was measured in mainstream smoke from bidi cigarettes at 2.13 to 25.9 ng per cigarette and from U.S. cigarettes at 34.3 to 139 ng per cigarette when smoked at an equal rate; however, bidi cigarettes generally are smoked at about twice the rate of U.S. cigarettes, resulting in delivery of about the same total amount of NNK to the smoker (Wu *et al.* 2004).

NNK may also form in the mouth during tobacco chewing or oral snuff use. Concentrations of NNK in the saliva of women who used snuff ranged from 2.1 to 201 ng/g. NNK was detected in pancreatic juices from smokers at a mean concentration of 88.7 ng/mL (compared with 12.4 ng/mL in nonsmokers) and in cervical mucus from smokers at 46.9 ng/g of mucus (Prokopczyk *et al.* 1997, 2002). Metabolites of NNK were found in the urine of newborns whose mothers had smoked during pregnancy, but not in the urine of those born to nonsmoking mothers (Lackmann *et al.* 1999). Children in households with smokers also had significantly elevated urinary concentrations of NNK metabolites; the highest levels were found among African-American children (Sexton *et al.* 2004). The concentration of NNK metabolites was also significantly increased in the urine of nonsmoking hospitality workers on days when they worked in locations where smoking was allowed (Tulunay *et al.* 2005). Reduction of smoking reduced the urinary levels of NNK metabolites, but the reduction was less than expected based on the reduction in the number of cigarettes smoked per day (Hecht *et al.* 2004, Joseph *et al.* 2005).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for N-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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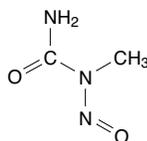
N-Nitroso-N-methylurea

CAS No. 684-93-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as nitrosomethylurea or N-methyl-N-nitrosourea



Carcinogenicity

N-Nitroso-N-methylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitroso-N-methylurea caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. It was carcinogenic in animals exposed perinatally or as adults. Perinatal exposure resulted mainly in nervous-system tumors, whereas tumors occurred at numerous tissue sites in adults, including the respiratory and digestive tracts.

Tumors of the nervous system were observed following prenatal exposure in rats, oral exposure in adult rats (peripheral nerves), and exposure by injection in newborn rats (peripheral nervous system) and adult rats, rabbits, and dogs (peripheral and central nervous system). Prenatal exposure also caused kidney tumors in rats and benign tumors of the lung (adenoma) and liver (hepatocellular adenoma) in mice, and exposed pregnant rats developed mammary-gland tumors (IARC 1972, 1978).

Administration of N-nitroso-N-methylurea by intratracheal instillation caused cancer of the nasopharyngeal tube, pharynx, larynx, bronchi, esophagus, forestomach, and trachea (epidermoid or large-cell anaplastic carcinoma) in hamsters. Intrarectal administration caused benign or malignant colon tumors (adenoma, adenocarcinoma, or squamous-cell carcinoma) in male rats and female mice and guinea pigs. In female mice, it also caused benign lung tumors (adenoma) and lymphoma. Lung tumors also resulted from exposure by injection in rats. In addition, injection exposure caused (1) digestive-tract tumors in rats, gerbils, and hamsters, (2) tumors of the pancreas, small intestine, and abdominal cavity in guinea pigs, (3) leukemia or lymphoma in newborn and adult mice and lymphoma in adult rats, (4) blood-vessel tumors in guinea pigs, rabbits, and dogs, (5) mammary-gland tumors in rats, and (6) tumors of the heart (sarcoma) and at the injection site in hamsters. Dermal exposure caused leukemia and benign and malignant skin tumors in mice and skin cancer (squamous or basal-cell carcinoma) in rats and hamsters. Intravesicular instillation caused benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) in female rats (IARC 1972, 1978).

Since N-nitroso-N-methylurea was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animal have been identified that confirmed the induction of several tumor types

previously observed and reported tumors at additional tissue sites, in additional species, and by additional routes of exposure:

- Tumors of the thymus were observed in rats following oral exposure (Lijinsky and Kovatch 1996).
- Tumors of the teeth (odontoma, odontoameloblastoma, and ameloblastoma) were observed in male rats exposed by injection (Smulow *et al.* 1983).
- Female shrews developed uterine and cervical tumors following intrarectal administration (Yang *et al.* 1996).
- In fish, addition of N-nitroso-N-methylurea to the tank water caused eye tumors (neuroblastoma) (Schwab *et al.* 1979).
- Placement of N-nitroso-N-methylurea-impregnated sutures in the ovaries of female rats caused benign or malignant ovarian tumors (adenoma or adenocarcinoma) (Tunca *et al.* 1985).
- Implantation of N-nitroso-N-methylurea, as well as injection, caused mammary-gland cancer (adenocarcinoma) in female rats (Thompson and Meeker 1983, Holtzman *et al.* 1985, Seaborn and Yang 1993, Takahashi *et al.* 1995).
- Administration of N-nitroso-N-methylurea directly into the stomach via a surgically formed external opening caused cancer of the forestomach (carcinoma) in rats of both sexes (Garcia-Gonzalez *et al.* 2000).

Oral administration, intrarectal administration, and injection of N-nitroso-N-methylurea in several species (adult monkeys, mice, rats, gerbils, or hamsters) caused tumors of the digestive tract (esophagus, glandular stomach, forestomach, small intestine, or colon) or respiratory tract (oropharynx or lung) (Adamson and Sieber 1979, Zimmerman *et al.* 1982, Eisenberg *et al.* 1983, Likhachey *et al.* 1983, Smulow *et al.* 1983, Yano *et al.* 1984, Wang *et al.* 1985, Verdeal *et al.* 1986, Beland *et al.* 1988, Bosland *et al.* 1992, Furukawa *et al.* 1992, Tatematsu *et al.* 1992, 1993, 1994, 1998, Lijinsky and Kovatch 1996, Tamano *et al.* 1996, Yang *et al.* 1996). Blood-vessel cancer (hemangioendothelial sarcoma) also was reported in mice (Tatematsu *et al.* 1993, 1998) and leukemia and tumors of the prostate, Zymbal gland, uterus, adrenal glands, and blood vessels in rats (Eisenberg *et al.* 1983, Verdeal *et al.* 1986, Bosland *et al.* 1992, Tamano *et al.* 1996).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to N-nitroso-N-methylurea.

Properties

N-Nitroso-N-methylurea is a nitrosamine compound that exists as a colorless to yellow crystal or plate at room temperature (HSDB 2009). It is soluble in water, alcohol, ether, acetone, benzene, chloroform, and other polar organic solvents and insoluble in nonpolar organic solvents. It decomposes in alkaline solution at a rate that depends on pH (IARC 1978). The pure compound is sensitive to moisture and light and should be stored under refrigeration. Physical and chemical properties of N-nitroso-N-methylurea are listed in the following table.

Property	Information
Molecular weight	103.1 ^a
Melting point	124°C (decomposes) ^a
Log <i>K</i> _{ow}	-0.03 ^a
Water solubility	14.4 g/L at 24°C ^a
Vapor pressure	0.0293 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitroso-*N*-methylurea was once widely used to synthesize diazomethane in the laboratory; however, it has been replaced by other reagents for this use (IARC 1972, 1978, HSDB 2009). *N*-Nitroso-*N*-methylurea has been studied as a chemotherapeutic agent in cancer treatment, either alone or in combination with cyclophosphamide. Small quantities are used in research to study its mutagenic effects on plants.

Production

N-Nitroso-*N*-methylurea has never been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

The potential for human exposure in the United States is limited, because *N*-nitroso-*N*-methylurea is not produced or used in large quantities (IARC 1978, HSDB 2009). Cancer patients potentially were directly exposed by injection when *N*-nitroso-*N*-methylurea was tested as a chemotherapeutic agent in conjunction with cyclophosphamide; however, no data were found on the frequency or extent of this testing (IARC 1978). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, two facilities released a total of 170 lb of *N*-nitroso-*N*-methylurea to the environment in 1999, 96% of which was from one facility. Releases totaled 260 lb in 2001 and 10 lb in 2005, 2006, and 2007 (TRI 2009). In air, *N*-nitroso-*N*-methylurea exists solely as vapor and is degraded by reaction with photochemically produced hydroxyl radicals, with an estimated half-life of 10 days. In water, it hydrolyzes, with a half-life of 1.2 hours at pH 7 at 20°C.

Occupational exposure to *N*-nitroso-*N*-methylurea may occur through inhalation or dermal contact at facilities where it is used in research (HSDB 2009). During clinical testing for its use as a chemotherapeutic agent, health professionals such as pharmacists, physicians, and nurses could have been exposed during preparation and administration of the drug or during clean-up (IARC 1978).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitroso-*N*-methylurea = U177.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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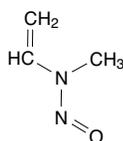
N-Nitrosomethylvinylamine

CAS No. 4549-40-0

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as *N*-methylvinylnitrosoamine



Carcinogenicity

N-Nitrosomethylvinylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosomethylvinylamine caused tumors in rats at several different tissue sites and by two different routes of exposure. Administration of *N*-nitrosomethylvinylamine in the drinking water caused cancer (carcinoma) of the tongue and pharynx and benign and malignant tumors of the esophagus (mainly squamous-cell carcinoma), and inhalation exposure caused cancer of the nasal cavity (squamous-cell carcinoma) (IARC 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosomethylvinylamine.

Properties

N-Nitrosomethylvinylamine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is soluble in water, lipids, and organic solvents. It is relatively unstable and decomposes in solution (up to 10% in 24 hours), and it is sensitive to light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosomethylvinylamine are listed in the following table.

Property	Information
Molecular weight	86.1 ^a
Boiling point	47°C to 48°C at 30 mm Hg ^b
Log <i>K</i> _{ow}	-0.28 ^b
Water solubility	30 g/L ^b
Vapor pressure	8.96 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-nitrosomethylvinylamine is used as a research chemical; no other uses were identified (IARC 1978, HSDB 2009).

Production

There is no evidence that *N*-nitrosomethylvinylamine has ever been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from one supplier worldwide, in the United States (ChemSources 2009).

Exposure

Exposure to *N*-nitrosomethylvinylamine is limited primarily to the individuals using it in research (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of *N*-nitrosomethylvinylamine occurred only in 1999 (157 lb), 2002 (10 lb), and 2003 (26 lb) (TRI 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosomethylvinylamine = P084.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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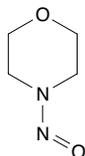
TRI. 2009. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. Last updated: 3/19/09. <http://www.epa.gov/triexplorer> and select *N*-Nitrosomethylvinylamine.

N-Nitrosomorpholine

CAS No. 59-89-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosomorpholine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosomorpholine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Tumors of the liver or bile duct were observed in several species and by several routes of exposure. Administration of *N*-nitrosomorpholine in the drinking water caused benign liver tumors (hepatocellular adenoma) in male mice and benign or malignant liver and bile-duct tumors (hepatocellular carcinoma, cholangiofibroma, or cholangiocarcinoma) in rats. Intravenous injection of *N*-nitrosomorpholine caused liver cancer (hepatocellular carcinoma) in rats, and addition of *N*-nitrosomorpholine to the tank water caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in two species of fish (IARC 1978).

Administration of *N*-nitrosomorpholine in the drinking water also caused benign lung tumors (adenoma) in male mice and blood-vessel cancer (hemangiosarcoma and hemangioendothelioma) and kidney tumors (epithelial tumors) in rats. Tumors of the respiratory tract (primarily the nasal cavities and trachea) and upper digestive tract occurred in hamsters of both sexes exposed by subcutaneous injection, and cancer of the nasal cavity in rats exposed by intravenous injection (IARC 1978).

Since *N*-nitrosomorpholine was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified, some of which reported induction of tumors by additional routes of exposure or at an additional tissue site:

- Administration of *N*-nitrosomorpholine in the drinking water or by stomach tube caused respiratory- or digestive-tract tumors in hamsters (Ketkar *et al.* 1983, Lijinsky *et al.* 1984, Cardesa *et al.* 1990).
- Inhalation exposure caused forestomach tumors in male rats, tracheal tumors in male hamsters, and liver tumors in female rats and male hamsters (Klein *et al.* 1990).
- Intratracheal instillation caused tracheal tumors in male hamsters (Ishinishi *et al.* 1988).
- Intravesicular instillation caused liver and nasal-cavity tumors in female rats (Lijinsky *et al.* 1991).
- Tumors of the esophagus occurred in female rats exposed to *N*-nitrosomorpholine in the drinking water (Lijinsky *et al.* 1988).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosomorpholine.

Properties

N-Nitrosomorpholine is a nitrosamine compound that exists as yellow crystals at room temperature (HSDB 2009). It is completely miscible with water and soluble in organic solvents. It is stable in the dark in neutral or alkaline solution for at least 14 days, but is less stable in more acidic solutions or in light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosomorpholine are listed in the following table.

Property	Information
Molecular weight	116.1 ^a
Melting point	29°C ^a
Boiling point	224°C to 224.5°C at 747 mm Hg ^a
Log <i>K</i> _{ow}	-0.44 ^a
Water solubility	1,000 g/L at 24°C ^b
Vapor pressure	0.036 mm Hg at 20°C ^b
Dissociation constant (p <i>K</i> _b)	12.41 ^c

Sources:^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

N-Nitrosomorpholine is used as a research chemical. Although it was found to be effective as an antimicrobial agent, and patents were issued for its use as a solvent for polyacrylonitrile and as an intermediate in the production of *N*-aminomorpholine, there is no evidence that it is used commercially in the United States (IARC 1978).

Production

There is no evidence that *N*-nitrosomorpholine is produced commercially in the United States. In 2009, it was available in small quantities for research purposes from nine U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrosomorpholine are dermal contact, ingestion, and inhalation (HSDB 2009). *N*-Nitrosamines are formed by reactions of precursors (nitrosating agents and primary or secondary amines) that are present in industrial processes, foods, or the human body (Schothorst and Somers 2005). *N*-Nitroso compounds have been identified in a variety of vegetables, fruits, cheeses, meats, and alcoholic beverages (Brunnemann *et al.* 1982b). *N*-Nitroso compounds may be formed from amines and quaternary ammonium salts by reaction with nitrosating agents, such as nitrite, in the stomach or during cooking processes. The degree of this potential exposure is unknown, but is assumed to be intermittent and at relatively low levels. *N*-Nitrosomorpholine was found in tobacco snuff at concentrations of 24 to 690 ppb (Brunnemann *et al.* 1982a) and in rubber nipples for baby bottles at 3.0 to 14.1 ppb (HSDB 2009). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 21 lb of *N*-nitrosomorpholine was released to the environment in 2005, of which 20 lb was released to a hazardous-waste landfill and 1 lb to an off-site hazardous-waste underground injection well (TRI 2009).

Workers in chemical research laboratories and in the rubber and tire manufacturing industry may be exposed to *N*-nitrosomorpholine. *N*-Nitrosomorpholine concentrations in air ranged from 0.07 to 5.1 µg/m³ in a tire factory and from 0.6 to 27 µg/m³ in an aircraft tire factory. *N*-Nitrosomorpholine was detected as a contaminant in analytical-grade dichloromethane at 10 to 32 µg/L and in chloroform at 2 to 376 µg/L (IARC 1978).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for N-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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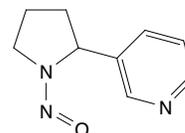
N-Nitrosornicotine

CAS No. 16543-55-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as NNN



Carcinogenicity

N-Nitrosornicotine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosornicotine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Administration of N-nitrosornicotine in the drinking water of rats of both sexes caused cancer of the nasal cavity (carcinoma in males and adenocarcinoma in females) and benign and malignant esophageal tumors (papilloma and carcinoma). Subcutaneous injection of N-nitrosornicotine caused benign tracheal tumors (papilloma) in hamsters of both sexes, and intraperitoneal injection caused benign lung tumors (adenoma) in mice of both sexes (IARC 1978).

Since N-nitrosornicotine was listed in the *Second Annual Report on Carcinogens*, additional experimental animal studies have been identified. N-Nitrosornicotine was reported to cause nasal tumors in rodents by the following additional routes of exposure: (1) by stomach tube or dietary exposure in male rats (IARC 1985, Gričute *et al.* 1986), (2) by administration in the drinking water and by intraperitoneal injection in hamsters of both sexes (IARC 1985), and (3) by subcutaneous injection in male rats, male hamsters, and female mink (IARC 1985, Koppang *et al.* 1992, 1997, IARC 2007). The types of nasal tumors varied among the studies, but mainly consisted of the malignant tumor esthesioneuroepithelioma (also known as olfactory neuroblastoma), which arises from the olfactory nerves, and benign tumors (mainly adenoma). In addition, exposure to N-nitrosornicotine by stomach tube or in the diet caused cancer of the esophagus (squamous-cell carcinoma) in male rats (IARC 1985, Gričute *et al.* 1986); subcutaneous injection caused benign lung tumors (adenoma) in rats of both sexes; and intraperitoneal injection caused benign tracheal tumors (papilloma) in male hamsters. N-Nitrosornicotine administered by oral swabbing (of the tongue or cheek pouch) caused tumors of the lung, forestomach, and liver in male mice and in hamsters of both sexes (Padma *et al.* 1989).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to N-nitrosornicotine.

Properties

N-Nitrosornicotine is a nitrosamine compound that exists as a yellow oil at room temperature, but solidifies on standing in the cold (HSDB 2009). It is soluble in water (ChemIDplus 2009). Physical and chemical properties of N-nitrosornicotine are listed in the following table.

Property	Information
Molecular weight	177.2 ^a
Melting point	47°C ^a
Boiling point	154°C at 0.2 mm Hg ^a
Log K_{ow}	0.32 ^b
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	0.2 mm Hg at 154°C ^a
Dissociation constant (pK_b)	8.84 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

The only known use of *N*-nitrosornicotine is as a research chemical (IARC 1985).

Production

There is no evidence that *N*-nitrosornicotine has been produced commercially in the United States (IARC 1985). In 2009, it was available in small quantities for research purposes from two U.S. suppliers (ChemSources 2009).

Exposure

N-Nitrosornicotine has been found in a variety of tobacco products (chewing tobacco, snuff, cigarettes, and cigars) and in mainstream and sidestream smoke from cigars and cigarettes, in the saliva of chewers of betel quid with tobacco, and in the saliva of oral-snuff users (IARC 1978, 1985). Some of the *N*-nitrosornicotine in saliva appears to be formed endogenously from nitrite in saliva and tobacco alkaloids. Thus, there is widespread exposure to *N*-nitrosornicotine among users of tobacco products and those exposed to sidestream smoke.

N-Nitrosornicotine is produced by nitrosation of nicotine during the curing, aging, processing, and smoking of tobacco. About half of the *N*-nitrosornicotine originates in the unburnt tobacco, whereas the remainder is formed during burning. *N*-Nitrosornicotine has been found in cigarettes at concentrations of up to 11.9 mg/kg, in snuff products at up to 77.1 mg/kg, and in chewing tobacco at up to 90.6 mg/kg. The differences in *N*-nitrosornicotine concentrations in tobacco products are largely due to differences in the tobacco types used in a given product, agricultural practices, curing methods, and manufacturing processes. *N*-Nitrosornicotine is formed primarily from its corresponding secondary amine (nornicotine) in the early stages of tobacco curing and processing. Some *N*-nitrosornicotine is formed from the tertiary amine (nicotine) at the later stages of tobacco curing and fermentation. Levels of *N*-nitrosornicotine are consistently higher in Burley than in Bright tobacco, regardless of the curing method. However, flue-curing of Bright tobacco produces nearly three times as much nitrosamine as air-curing of the same tobacco. *N*-Nitrosornicotine has been found in cigarette smoke at up to 3.7 µg per cigarette (IARC 1978, 1985).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

References

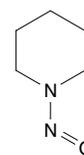
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N-Nitrosopiperidine

CAS No. 100-75-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosopiperidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrosopiperidine caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Tumor occurred mainly in the respiratory tract, upper digestive tract, and liver (IARC 1978). Benign lung tumors (adenoma) occurred in mice administered *N*-nitrosopiperidine in the diet or drinking water or by intraperitoneal injection. Benign and malignant nasal-cavity tumors (cholesteatoma, esthesioneuroepithelioma, and squamous-cell carcinoma) and cancer of the pharynx (carcinoma) were observed in rats exposed by subcutaneous or intravenous injection. When administered as a single dose to pregnant hamsters, *N*-nitrosopiperidine caused respiratory-tract tumors at a much higher

incidence in the mothers than in the offspring. Upper-digestive-tract tumors caused by *N*-nitrosopiperidine included cancer of the fore-stomach (squamous-cell carcinoma) and benign esophageal tumors (papilloma) following dietary administration to male mice and benign and malignant esophageal tumors (papilloma and squamous-cell carcinoma) in rats exposed via the drinking water or by subcutaneous or intravenous injection. Benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma) occurred in male mice administered *N*-nitrosopiperidine in the diet and rats and monkeys administered *N*-nitrosopiperidine in the drinking water. Tumors of the respiratory tract, upper digestive tract, and liver also occurred in hamsters administered *N*-nitrosopiperidine by subcutaneous injection. One study reported blood-vessel cancer (hemangioendothelioma) in male mice exposed to *N*-nitrosopiperidine in the diet.

Since *N*-nitrosopiperidine was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. *N*-Nitrosopiperidine administered in the drinking water caused benign and malignant upper-respiratory-tract tumors in hamsters of both sexes (Cardesa *et al.* 1990) and liver cancer (hepatocellular carcinoma) in monkeys exposed by intraperitoneal injection or dietary administration (Adamson and Sieber 1979).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosopiperidine.

Properties

N-Nitrosopiperidine is a nitrosamine compound that exists as a yellow oil at room temperature (HSDB 2009). It is soluble in water, hydrochloric acid, organic liquids, and lipids. Physical and chemical properties of *N*-nitrosopiperidine are listed in the following table.

Property	Information
Molecular weight	114.2 ^a
Specific gravity	1.0631 at 18.5°C/4°C ^a
Boiling point	219°C ^a
Log <i>K</i> _{ow}	0.36 ^a
Water solubility	76.5 g/L at 24°C ^b
Vapor pressure	0.092 mm Hg at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosopiperidine is used as a research chemical (HSDB 2009); no other uses were identified.

Production

N-Nitrosopiperidine was first prepared in 1863 by the action of nitrogen dioxide on piperidine (IARC 1978). Although numerous patents have been issued for the production of *N*-nitrosopiperidine, there is no evidence that it has been manufactured commercially in the United States. In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009). No other data on U.S. production, imports, or exports of *N*-nitrosopiperidine were found.

Exposure

Because only small quantities of *N*-nitrosopiperidine are produced for research, potential exposure appears to be limited. The general population may be exposed to low concentrations of *N*-nitrosopiperidine from cigarette smoke and certain foods (IARC 1978). Trace amounts of *N*-nitrosopiperidine were found in cigarettes, but it was not found in all brands of cigarettes tested. *N*-Nitrosopiperidine was found at

concentrations of up to 64 µg/kg in meat and fish products such as bacon, bologna, wieners, and smoked cod. The presence of *N*-nitrosopiperidine in meat, cheese, and spices results from the preservative use of sodium nitrite, which reacts with the amines present in meats and cheese to form nitrosamines. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of *N*-nitrosopiperidine were 14,756 lb in 1999 and 19,309 lb in 2001; most was released to on-site hazardous-waste landfills, and a small portion was released to off-site non-hazardous-waste landfills. In 2002 and thereafter, much smaller total quantities (≤ 500 lb) were released to off-site hazardous-waste landfills (TRI 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosopiperidine = U179.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premises, a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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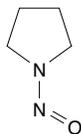
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N-Nitrosopyrrolidine

CAS No. 930-55-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrosopyrrolidine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to *N*-nitrosopyrrolidine caused tumors in two rodent species and at two different tissue sites. Administered in the drinking water, it caused liver cancer (hepatocellular carcinoma) in several strains of rats (both sexes) and benign lung tumors (adenoma) in mice of both sexes (IARC 1978).

Since *N*-nitrosopyrrolidine was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Liver tumors were observed in hamsters exposed to *N*-nitrosopyrrolidine in the drinking water; tumor incidence increased with increasing dose (Ketkar *et al.* 1982). *N*-Nitrosopyrrolidine administered by intraperitoneal injection to hamsters caused tumors of the larynx or trachea 25 weeks after a single injection and preneoplastic and neoplastic nasal-cavity lesions 25 weeks after two injections. In female strain A/J mice (a strain with a high spontaneous incidence of lung tumors), *N*-nitrosopyrrolidine administered by intraperitoneal injection increased the incidence of benign lung tumors and the number of tumors per animal (Hecht *et al.* 1988, Hoffmann *et al.* 1993).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosopyrrolidine.

Properties

N-Nitrosopyrrolidine is a nitrosamine compound that is a yellow liquid at room temperature (HSDB 2009). It is totally soluble in water, organic liquids, and lipids. It is stable at room temperature in the dark, but is sensitive to light, especially ultraviolet light (IARC 1978). Physical and chemical properties of *N*-nitrosopyrrolidine are listed in the following table.

Property	Information
Molecular weight	100.1 ^a
Specific gravity	1.1 ^a
Boiling point	214°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	-0.19 ^a
Water solubility	1,000 g/L at 24°C ^b
Vapor pressure	0.06 at 20°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrosopyrrolidine is used primarily as a research chemical and is not produced commercially in the United States (IARC 1978, HSDB 2009).

Production

N-Nitrosopyrrolidine was first prepared in 1888 by the reaction of pyrrolidine with potassium nitrate in a weak hydrochloric acid solution (IARC 1978). It is not produced commercially in the United States. In 2009, it was available in small quantities for research purposes from eight U.S. suppliers (ChemSources 2009).

Exposure

N-Nitrosopyrrolidine is produced when foods preserved with or contaminated by nitrite, especially fatty foods, are prepared by heating. Exposure can occur through inhalation of vapors released during cooking or ingestion of food (IARC 1978). In recent years, lower concentrations of sodium nitrite in foods have resulted in lower concentrations of *N*-nitrosopyrrolidine in foods. For example, the *N*-nitrosopyrrolidine content of bacon decreased from approximately 67 µg/kg in 1971 through 1974 to 17 µg/kg in 1975 and 1976; when bacon is fried, an average of 50% of the *N*-nitrosopyrrolidine normally present in the meat is detected in the vapor. Dry premixed cures containing spices and sodium nitrite originally contained *N*-nitrosopyrrolidine at a concentration of 40 µg/kg, but the level increased to 520 µg/kg after six months of storage. *N*-Nitrosopyrrolidine was found in tobacco smoke at concentrations of up to 0.113 µg per cigarette and in pipe-bowl scrapings at up to 1.6 mg/kg of residue. Wastewater from chemical factories was reported to contain *N*-nitrosopyrrolidine at concentrations of 0.09 to 0.20 µg/L.

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.016 µg/L; based on fish or shellfish consumption only = 34 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of *N*-nitrosopyrrolidine = U180.

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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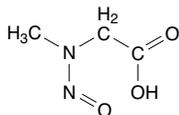
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N-Nitrososarcosine

CAS No. 13256-22-9

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

N-Nitrososarcosine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

N-Nitrososarcosine caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary exposure to *N*-nitrososarcosine caused cancer of the nasal cavity (squamous-cell carcinoma) in mice of both sexes, and administration in the drinking water caused benign and malignant tumors of the esophagus (papilloma and squamous-cell carcinoma) in rats. Intraperitoneal injection of *N*-nitrososarcosine in newborn mice caused liver cancer (hepatocellular carcinoma) in males (IARC 1978).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrososarcosine.

Properties

N-Nitrososarcosine is a nitrosamine compound that is a pale-yellow crystal at room temperature (HSDB 2009). It is soluble in water and polar organic solvents but is unstable in aqueous solution. It is sensitive to light, especially ultraviolet light (Akron 2009). Physical and chemical properties of *N*-nitrososarcosine are listed in the following table.

Property	Information
Molecular weight	118.1 ^a
Melting point	66°C to 67°C ^a
Log <i>K</i> _{ow}	-0.78 ^b
Water solubility	1,000 g/L at 25°C ^b
Vapor pressure	0.00261 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

N-Nitrososarcosine is not used commercially in the United States, but has limited use in research (IARC 1978, HSDB 2009).

Production

There is no evidence that *N*-nitrososarcosine has been produced commercially in the United States (IARC 1978, HSDB 2009). In 2009, it was available in small quantities for research purposes from three U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to *N*-nitrososarcosine are inhalation, ingestion, and dermal contact (HSDB 2009). *N*-Nitrososarcosine is formed when nitrite-preserved foods containing primary or secondary amines are prepared by heating. Exposure could occur through inhalation during cooking or through ingestion of the prepared food. *N*-Nitrososarcosine has been detected in foods; in particular, it was found in smoked meat at concentrations of 2 to 56 µg/kg. It was also found in tobacco smoke at concentrations of 22 to 460 ng per cigarette. In air, *N*-nitrososarcosine exists predominantly in the gas phase and degrades by reaction with photochemically produced hydroxyl radicals, with a half-life of 1.9 days (IARC 1978, Tricker *et al.* 1991, HSDB 2009).

Regulations

Consumer Product Safety Commission (CPSC)

A voluntary standard provides that rubber pacifiers shall not contain more than 10 ppb of any single nitrosamine or more than 20 ppb of total nitrosamines.

Environmental Protection Agency (EPA)

Clean Water Act

Effluent Guidelines: Nitrosamines are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0008 µg/L for nitrosamines; based on fish or shellfish consumption only = 1.24 µg/L for nitrosamines.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Toxic Substances Control Act

Nitrosating agents distributed in commerce require warning labels and instructions on use.

Food and Drug Administration (FDA)

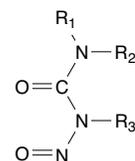
The action level for *N*-nitrosamines in rubber baby-bottle nipples is 10 ppb.

In order to use nitrites and/or nitrates as food additives in curing premixes a petition must be filed supported by data demonstrating that nitrosamines are not formed.

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Nitrosourea Chemotherapeutic Agents



Generic nitrosourea structure

Introduction

Five nitrosourea chemotherapeutic agents are listed in the Report on Carcinogens as individual chemicals and not as a class. The generic structure for a nitrosourea is shown above (the simplest member of the nitrosourea class, *N*-nitrosourea, has hydrogen atoms for the R₁, R₂, and R₃ groups). The five nitrosourea chemotherapeutic agents share

a common mechanism of action for their cytotoxicity and antitumor activity, which result from their nonenzymatic decomposition to produce products with alkylating and carbamoylating activities (Lemoine *et al.* 1991, Chabner *et al.* 2001). The 2-chloroethylnitrosoureas (CENUs) — 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU, lomustine), bis(chloroethyl) nitrosourea (BCNU, carmustine), 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU, semustine), and chlorozotocin — degrade to form the 2-chloroethyl carbonium ion, which is a strong electrophile capable of alkylating guanine, cytidine, and adenine. If the chloride atom is displaced, intra- or inter-strand cross-links of DNA can result. Interstrand cross-links are considered to be associated with the cytotoxicity of nitrosoureas. Streptozotocin differs from the other four nitrosourea compounds in that it does not contain the 2-chloroethylnitrosourea group. Spontaneous degradation of nitrosourea compounds also can produce organic isocyanates that can carbamoylate lysine residues of proteins, and this reaction may inactivate some DNA repair enzymes. Of these five nitrosoureas, chlorozotocin and streptozotocin have low carbamoylating activity.

One of the nitrosourea compounds, methyl-CCNU, is listed as *known to be a human carcinogen*, and CCNU, BCNU, chlorozotocin, and streptozotocin are listed as *reasonably anticipated to be a human carcinogen*. In addition, two nitrosamines that share the nitrosourea structure, *N*-nitroso-*N*-methylurea and *N*-nitroso-*N*-ethylurea (see their profiles under Nitrosamines) are also listed as *reasonably anticipated to be a human carcinogen*.

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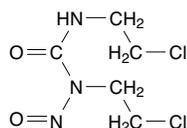
Bis(chloroethyl) Nitrosourea

CAS No. 154-93-8

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as BCNU, carmustine, or *N,N'*-bis(2-chloroethyl) nitrosourea



Carcinogenicity

Bis(chloroethyl) nitrosourea (BCNU) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to BCNU by injection caused tumors in rats and mice at several different tissue sites. Lung tumors resulted from intraperitoneal injection of BCNU in rats of both sexes or intravenous injection in male rats, and tumors in the peritoneal cavity also were observed in male rats following intraperitoneal injection. Dermal exposure of mice to BCNU caused an early appearance of skin tumors induced by exposure to ultraviolet B radiation (IARC 1981, 1982).

Since BCNU was listed in the *Fourth Annual Report on Carcinogens*, an additional study in rats has been identified, in which BCNU administered by intravenous injection caused lung cancer (adenocar-

cinoma) and increased the incidence of neurogenic tumors (oligodendroglioma) (Eisenbrand 1984, Habs and Schmähl 1984).

Cancer Studies in Humans

The data available from studies in humans were inadequate to evaluate the relationship between human cancer and exposure specifically to BCNU. No epidemiological studies have evaluated exposure only to BCNU. However, BCNU is associated with the development of acute nonlymphocytic leukemia following its use with other anticancer therapies in the treatment of preexisting cancer (IARC 1987).

Properties

BCNU is bifunctional alkylating agent that is used as an antineoplastic agent. It is a chloroethyl nitrosourea compound that is an orange-yellow to light-yellow powder at room temperature (IARC 1981, Chabner *et al.* 2001, Akron 2009). BCNU is only slightly soluble in water and 50% ethanol, but is soluble in ethanol and lipids. It is sensitive to oxidation and hydrolysis at neutral pH with a half life of 98 minutes (IARC 1981). Physical and chemical properties of BCNU are listed in the following table.

Property	Information
Molecular weight	214.0 ^a
Melting point	31°C ^b
Log K_{ow}	1.53 ^b
Water solubility	4 g/L at 25°C ^b
Vapor pressure	3.69×10^{-5} mm at Hg 25°C ^b
Dissociation constant (pK_a)	10.19 ^a

Sources: ^aAkron 2009, ^bChemIDplus 2009.

Use

BCNU has been used since 1971 as an anticancer drug and in 1977 was approved by the U.S. Food and Drug Administration, as carmustine, to be marketed for the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, and primary or metastatic brain tumors (IARC 1981, FDA 2009a, MedlinePlus 2009). It has also been used to treat malignant melanoma, breast cancer, gastrointestinal cancer, Ewing's sarcoma, and Burkitt's lymphoma and to be applied to the skin to treat mycosis fungoides (MedlinePlus 2009). BCNU may be used alone or in combination with other antineoplastic agents (ClinicalTrials 2009).

Production

No data on production volumes of BCNU were found. In 2009, BCNU was available from nine suppliers worldwide, including seven U.S. suppliers (ChemSources 2009). Carmustine is the active ingredient in two pharmaceutical products, an intracranial implant and an injectable drug, which are available from two different pharmaceutical companies (FDA 2009b). The injectable product is available in 100-mg vials, and the implantable product comes in a 7.7-mg size.

Exposure

The primary routes of human exposure to BCNU are injection, implantation (FDA 2009b), and dermal contact in patients (MedlinePlus 2009). Reported doses of the injectable drug are 100 to 250 mg/m² of body surface area daily by intravenous injection for two or three days (IARC 1981). In 2009, 159 clinical trials involving BCNU alone or in combination with other antineoplastic agents and treatments were in progress or recently completed (ClinicalTrials 2009). Health professionals and support staff (including custodians) may be exposed to BCNU by dermal contact, inhalation, and accidental ingestion during drug preparation, administration, or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH

2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 14,122 health-services workers, including 10,338 women, potentially were exposed to BCNU (NIOSH 1990).

Regulations

Food and Drug Administration (FDA)

Carmustine is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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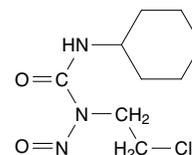
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea

CAS No. 13010-47-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as CCNU or lomustine



Carcinogenicity

1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to CCNU by injection caused tumors in rodents. Lung tumors resulted from intraperitoneal injection of CCNU in rats of both sexes or intravenous injection in male rats (IARC 1981, 1982). Following intraperitoneal injection of CCNU, a slight increase in the incidence of malignant lymphoma (lymphosarcoma) was observed in mice of both sexes.

Cancer Studies in Humans

The data available from studies in humans were inadequate to evaluate the relationship between human cancer and exposure specifically to CCNU. In several reported cases, cancer patients who received CCNU developed leukemia; however, all but one of these patients had also been treated with other cytotoxic agents and/or irradiation (IARC 1981, 1982).

Properties

CCNU is a bifunctional alkylating agent that is used as an antineoplastic agent. It is a chloroethyl nitrosourea compound that is a yellow powder at room temperature. It is practically insoluble in water, soluble in ethanol, 0.1 N hydrochloric acid, and sodium hydroxide, and highly soluble in lipids. It may be oxidized or hydrolyzed at room temperature and neutral pH with a half-life of 117 minutes (IARC 1981, 1987, HSDB 2009). Physical and chemical properties of CCNU are listed in the following table.

Property	Information
Molecular weight	233.7 ^a
Melting point	88°C to 90°C ^b
Log K_{ow}	2.83 ^b
Water solubility	111 mg/L at 25°C ^b
Vapor pressure	1.01×10^{-5} mm Hg at 25°C ^b

Sources: ^aHSDB 2009; ^bChemIDplus 2009.

Use

CCNU is an oral anticancer drug that was approved by the U.S. Food and Drug Administration in 1976 for marketing, as lomustine (FDA 2009a). CCNU is used alone or in combination with other antineoplastic agents, including procarbazine and vincristine, etoposide and prednimustine, and other combinations (IARC 1981, HSDB 2009). It is used primarily in the treatment of Hodgkin's disease and brain tumors, but it has also been used to treat other cancer, includ-

ing lung cancer, non-Hodgkin's lymphoma, malignant melanoma, breast cancer, kidney cancer, and cancer of the gastrointestinal tract (MedlinePlus 2009). It has also been applied to the skin to treat mycosis fungoides and psoriasis.

Production

CCNU was first synthesized in 1966 (IARC 1981). In 2009, it was produced by two manufacturers, one in China and one in Europe (SRI 2009), and was available from eighteen suppliers, including nine U.S. suppliers (ChemSources 2009). CCNU (lomustine) is the active ingredient in three products (capsules in strengths of 10, 40, and 100 mg) from a single pharmaceutical company (FDA 2009b).

Exposure

The primary route of human exposure to CCNU is ingestion during its use as a pharmaceutical product; however, exposure potentially can also occur through inhalation and dermal contact (Akron 2009, MedlinePlus 2009). The recommended dose for adults and children is 130 mg/m² of body surface, given as a single oral dose every six weeks (IARC 1981). In 2009, 45 clinical trials involving CCNU were in progress or recently completed, including 12 that had not completed patient recruitment (ClinicalTrials 2009). Health professionals and support staff (including custodians) may be exposed by dermal contact, inhalation, or accidental ingestion during drug preparation, administration, or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,457 health-services workers, including 1,069 women, potentially were exposed to CCNU (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Lomustine is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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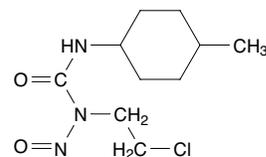
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea

CAS No. 13909-09-6

Known to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as methyl-CCNU, MeCCNU, or semustine



Carcinogenicity

1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (methyl-CCNU) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

An increased relative risk (over 12-fold) for nonlymphocytic leukemia was found among patients with gastrointestinal cancer who were treated with methyl-CCNU in several clinical trials; 14 cases of leukemic disorders were reported among 2,067 patients given methyl-CCNU, compared with only 1 case of acute nonlymphocytic leukemia among 1,566 patients given other therapies (Boice *et al.* 1983). A later analysis of this study found that the risk of leukemia increased with increasing cumulative dose of methyl-CCNU, reaching a relative risk of about 40-fold, adjusted for survival time, among patients treated with the highest dose (Boice *et al.* 1986, IARC 1987).

Cancer Studies in Experimental Animals

There is limited evidence for the carcinogenicity of methyl-CCNU in experimental animals (Weisburger 1977). Methyl-CCNU administered by intravenous injection caused lung tumors in male rats. Administered by intraperitoneal injection, it increased the total incidence of all tumors in male rats and slightly increased the incidence of leukemia and malignant lymphoma (lymphosarcoma) in female mice (IARC 1987).

Properties

Methyl-CCNU is a direct-acting bifunctional alkylating agent that has been tested for use as an antineoplastic agent. It is a chloroethyl

nitrosourea compound that is a light-yellow powder at room temperature (IARC 1987, Akron 2009). It is practically insoluble in water (ChemIDplus 2009). Physical and chemical properties of methyl-CCNU are listed in the following table.

Property	Information
Molecular weight	247.7 ^a
Melting point	70°C ^b
Log K_{ow}	3.3 ^a
Water solubility	0.037 g/L at 25°C ^a
Vapor pressure	5.61×10^{-6} mm Hg at 25°C ^a

Sources: ^aChemIDplus 2009, ^bAkron 2009.

Use

Methyl-CCNU is an investigational chemotherapy drug that has been used in clinical trials to treat several types of cancer, including brain cancer, malignant melanoma, lung cancer, and gastrointestinal-tract cancer (Boice *et al.* 1983). As of 2009, it had not been approved by the U.S. Food and Drug Administration for any uses (FDA 2009).

Production

No data on U.S. production, imports, or exports of methyl-CCNU were found. In 2009, methyl-CCNU was available from eight suppliers worldwide, including six U.S. suppliers (ChemSources 2009).

Exposure

The most direct exposure to methyl-CCNU is of cancer patients participating in clinical trials of treatment regimens that include methyl-CCNU. In 2009, two completed clinical trials involving methyl-CCNU were identified (ClinicalTrials 2009). The typical oral dose is 125 to 200 mg/m² of body surface area, repeated every six weeks (Parfitt 1999). Health professionals and support staff (including custodians) may be exposed to methyl-CCNU by dermal contact, inhalation, or accidental ingestion during drug preparation, administration, or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 229 workers, including 82 women, potentially were exposed to methyl-CCNU (NIOSH 1990).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to methyl-CCNU were identified.

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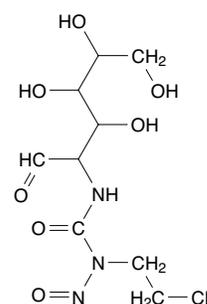
Zimmerman PF, Larsen RK, Barkley EW, Gallelli JF. 1981. Recommendations for the safe handling of injectable antineoplastic drug products. *Am J Hosp Pharm* 38(11): 1693-1695.

Chlorozotocin

CAS No. 54749-90-5

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

Chlorozotocin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and because it is a member of a well-defined, structurally related class of substances listed in the Report on Carcinogens as either *known to be a human carcinogen* or *reasonably anticipated to be a human carcinogen*.

Cancer Studies in Experimental Animals

Exposure to chlorozotocin caused tumors at several different tissue sites in rats. Chlorozotocin administered to male rats by intravenous injection caused cancer of the nervous system, lungs, and forestomach. Intraperitoneal injection of chlorozotocin caused tumors in the abdominal cavity (sarcoma or mesothelioma) in rats of both sexes (IARC 1990).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to chlorozotocin.

Studies on Mechanisms of Carcinogenesis

Chlorozotocin is structurally related to other chloroethyl nitrosoureas, one of which, 1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea, is listed in the Report on Carcinogens as *known to be a human carcinogen*, and two of which, bis(chloroethyl) nitrosourea and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. Chlorozotocin exerts its adverse effects through the formation of mono- and bi-functional alkylating agents. It causes genetic damage in a wide variety of bacterial and mammalian cellular assays, inducing mutations in bacteria, yeast, insects, and cultured mammalian cells and DNA damage in human, mouse, and Chinese ham-

ster cells *in vitro* and in bone-marrow cells in rats exposed *in vivo* (IARC 1990). In rats subcutaneously implanted with rhabdomyosarcoma cells, chlorozotocin administered by intraperitoneal injection increased metastasis to the lungs (Pauwels *et al.* 1985). There is no evidence to suggest that the mechanisms by which chlorozotocin causes tumors in experimental animals would not also operate in humans.

Properties

Chlorozotocin is a nitrosourea compound that exists as ivory-colored crystals at room temperature. It is soluble in water and is stable in solution at room temperature for up to 3 hours and under refrigeration for 24 hours. The powder form of chlorozotocin is stable under refrigeration for two years. The spontaneous, nonenzymatic degradation of chlorozotocin results in formation of DNA-alkylating and protein-carbamoylating moieties (Chabner *et al.* 2001). Physical and chemical properties of chlorozotocin are listed in the following table.

Property	Information
Molecular weight	265.7 ^a
Melting point	147°C to 148°C (decomposes with evolution of gas) ^b
Log K_{ow}	-1.02 ^b
Water solubility	1.8 g/L at 25°C ^a
Vapor pressure	3.98×10^{-14} mm Hg at 25°C ^a
Dissociation constant (pK_a)	9.08 ^c

Sources: ^aChemIDplus 2009, ^bHSDB 2009, ^cAkron 2009.

Use

Chlorozotocin is a cytostatic agent that has been used to treat melanoma and multiple myeloma and cancer of the stomach, large intestine, pancreas, and lung (IARC 1990).

Production

Synthesis of chlorozotocin occurs by nitrosation of the urea derivative prepared from D-glucosamine and 2-chloroethyl isocyanate. Chlorozotocin was reported to be produced in the United States (IARC 1990), but no production data were found, nor any data on U.S. imports or exports of chlorozotocin, and no U.S. suppliers were identified. As of 2009, no products containing chlorozotocin as an active ingredient had been approved for use by the U.S. Food and Drug Administration (FDA 2009).

Exposure

The primary route of potential human exposure to chlorozotocin is intravenous administration. Chlorozotocin has been given intravenously at doses of 100 to 225 mg/m² of body surface area (IARC 1990). Health professionals and support staff (including custodians) may be exposed to chlorozotocin by dermal contact, inhalation, or accidental ingestion during drug preparation, administration, or cleanup of medical waste, including excretions from treated patients (NIOSH 2004, Zimmerman *et al.* 1981). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 267 health-services workers, including 223 women, potentially were exposed to chlorozotocin (NIOSH 1990).

Regulations

No specific regulations or guidelines relevant to reduction of exposure to chlorozotocin were identified.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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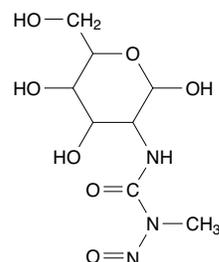
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Streptozotocin

CAS No. 18883-66-4

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Streptozotocin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to streptozotocin by injection caused tumors at several different tissue sites in three rodent species. Administration of streptozotocin by intraperitoneal injection caused kidney tumors in rats and mice of both sexes. In mice, it also caused lung tumors in both sexes and uterine tumors in females. In rats, it also caused pancreatic tumors in both sexes, liver tumors in females, and cancer of the abdominal cavity (sarcoma of the peritoneum) in males. In hamsters, it caused tumors of the liver (hepatocellular carcinoma) or bile duct (cholangioma) in both sexes (IARC 1978). A single intravenous injection of streptozotocin caused malignant or benign kidney tumors (adenocarcinoma, sarcoma, or adenoma) in rats of both sexes (IARC 1974, 1978, Rakietyen and Gordon 1975).

Since streptozotocin was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Intravenous injection of streptozotocin increased the incidence of benign or malignant kidney tumors in mice of both sexes (Hard 1985, Delahunt *et al.* 1995) and the incidence of benign tumors of the kidney, pancreas, liver, bile duct, and testis in male rats (Feldman *et al.* 1977, Kazumi *et al.* 1978, Okawa and Doi 1983). Pancreatic tumors (islet-cell adenoma, ductular adenoma, or insulinoma) also were observed in hamsters of both sexes after a single intravenous injection of streptozotocin (Pour and Patil 1983) and in male hamsters after intraperitoneal injection (Pour *et al.* 1990).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to streptozotocin.

Properties

Streptozotocin is a nitrosourea compound that exists as pale-yellow or ivory pointed platelets or prisms at room temperature (HSDB 2009). It is soluble in water, lower alcohols, and ketones, slightly soluble in most other polar organic solvents, and insoluble in nonpolar organic solvents. Streptozotocin is sensitive to humidity and light and decomposes rapidly at temperatures over 70°C (IARC 1974). It is most stable in acidic solutions and decomposes rapidly in alkaline solutions. Physical and chemical properties of streptozotocin are listed in the following table.

Property	Information
Molecular weight	265.2 ^a
Melting point	115°C ^b
Log K_{ow}	-1.45 ^b
Water solubility	5.070 g/L at 25°C ^b
Vapor pressure	1.74×10^{-12} mm Hg at 25°C ^b
Dissociation constant (pK_a)	1.35 ^a

Sources: ^aHSDB 2009; ^bCHEMIDplus 2009.

Use

Streptozotocin was approved by the U.S. Food and Drug Administration in 1982, as Zanosar, to be marketed for treatment of pancreatic cancer (FDA 2009a). It has also been used to induce and study diabetes, because it has a specific toxic action on pancreatic β -cells (IARC 1974, 1978). Streptozotocin has been investigated as a potential antibacterial agent, but has never been used commercially for this purpose. It is used to treat pancreatic islet-cell cancer, pancreatic adenocarcinoma, Hodgkin's disease, colorectal cancer, liver cancer (hepatocellular carcinoma), adrenal-gland cancer (pheochromocytoma), lung cancer (epidermoid carcinoma), lymphocytic lymphoma, Burkitt's lymphoma, acute lymphocytic leukemia, malignant melanoma, metastatic sarcoma, and malignant carcinoid tumors (IARC 1978, MedlinePlus 2009).

Production

Streptozotocin is derived from the bacterium *Streptomyces achromogenes* and has been synthesized by three different procedures (IARC 1978, HSDB 2009). In 2009, it was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 24 suppliers, including 15 U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of streptozotocin were found.

Exposure

Streptozotocin is available as an injectable product in 1-g vials from a single U.S. pharmaceutical company (FDA 2009b). In 2009, eight

clinical trials using streptozotocin in combination with other antineoplastic agents as treatment for pancreatic, brain, colorectal, adrenal cortical, or various other endocrine tumors were in progress or recently completed (ClinicalTrials 2009). Health professionals and support staff (including custodians) may be exposed to streptozotocin by dermal contact, inhalation, or accidental ingestion during drug preparation, administration, or cleanup of medical waste, including excretions from treated patients (Zimmerman *et al.* 1981, NIOSH 2004). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,074 workers, including 1,713 women, potentially were exposed to streptozotocin (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 1 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of streptozotocin = U206.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Streptozotocin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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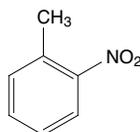
o-Nitrotoluene

CAS No. 88-72-2

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)

Also known as 2-nitrotoluene



Carcinogenicity

o-Nitrotoluene is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data on mechanisms of carcinogenesis.

Cancer Studies in Experimental Animals

Oral exposure to *o*-nitrotoluene caused tumors at several different tissue sites in rats and mice and early onset of cancer in male rats. Malignant mesothelioma and mesothelial-cell hyperplasia of the tunica vaginalis of the epididymis were observed in male rats administered *o*-nitrotoluene in their feed for 13 weeks (NTP 1992). Bile-duct cancer (cholangiocarcinoma) was observed after 26 weeks, both in rats exposed to *o*-nitrotoluene for 26 weeks and in rats exposed for 13 weeks and then observed for 13 more weeks without exposure (NTP 1996). *o*-Nitrotoluene caused cancer at several tissue sites in two-year chronic exposure studies of rats and mice of both sexes and in a study in which male rats were exposed to *o*-nitrotoluene for 13 weeks and evaluated at two years (NTP 2002). In rats, *o*-nitrotoluene caused (1) subcutaneous skin tumors and mammary-gland tumors (fibroadenoma) in both sexes, (2) malignant mesothelioma and benign or malignant tumors of the liver (hepatocellular adenoma or carcinoma or cholangiocarcinoma) and lung (alveolar/bronchiolar adenoma or carcinoma) in males, and (3) benign liver tumors (hepatocellular adenoma) in females. In mice, it caused malignant blood-vessel tumors (hemangiosarcoma) in both sexes, malignant tumors of the large intestine (cecal carcinoma) in males, and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in females (NTP 2002).

Studies on Mechanisms of Carcinogenesis

Following oral administration to rats and mice, *o*-nitrotoluene is absorbed into the blood and rapidly cleared; the serum half-life is 1.5 hours in rats (NTP 2002). In the rat liver, *o*-nitrotoluene is metabolized to *o*-nitrobenzyl alcohol and can follow several metabolic pathways: (1) glucuronidation to *o*-nitrobenzyl glucuronide,

(2) sulfation and subsequent reaction with glutathione and acetylcysteine to *o*-nitrobenzyl sulfate, *S*-(*o*-nitrobenzyl)glutathione, and *S*-(*o*-nitrobenzyl)-*N*-acetylcysteine, or (3) metabolism to *o*-aminobenzyl alcohol followed by oxidation to *o*-aminobenzoic acid. The metabolites are eliminated primarily in the urine. The major metabolites are *o*-nitrobenzyl glucuronide and *o*-nitrobenzoic acid major metabolites in rats and mice and *o*-aminobenzyl alcohol and *S*-(*o*-nitrobenzyl)-*N*-acetylcysteine in rats. Female rats excrete less than half as much of the dose in the form of *o*-aminobenzyl alcohol, *o*-nitrobenzyl alcohol, or *S*-(*o*-nitrobenzyl)-*N*-acetylcysteine as male rats (NTP 2002). The glucuronidated form can also be excreted in the bile; when the glucuronidated form in the bile is excreted into the small intestine, intestinal bacteria can deconjugate it and reduce the nitro group to an amino group, forming aminobenzyl alcohol. Aminobenzyl alcohol can be reabsorbed from the intestine and further metabolized by the liver to reactive compounds (carbonium and nitrenium ions) that can covalently bind to DNA or to proteins (Chism and Rickert 1985, NTP 2002, 2008). Thus, microbial metabolism in the intestine is an important step in the carcinogenicity of *o*-nitrotoluene. However, neither *o*-aminobenzyl alcohol nor its metabolites have been detected in mouse urine after exposure to *o*-nitrotoluene (NTP 2002); therefore, other unidentified biochemical pathways leading to tumor formation most likely are involved.

o-Nitrotoluene did not cause mutations in bacteria. In studies of its ability to cause genetic damage in cultured mammalian cells, the results were mixed. *o*-Nitrotoluene caused (1) sister chromatid exchange in Chinese hamster ovary (CHO) cells, (2) chromosomal aberrations in Chinese hamster lung (CHL) cells and human peripheral lymphocytes but not in CHO cells, (3) micronucleus formation in CHL cells but not in CHO-K1 cells, and (4) DNA damage in L5178Y mouse lymphoma cells (NTP 2008). It did not induce DNA repair in rat or human hepatocytes (NTP 2008). In rats and mice exposed *in vivo*, *o*-nitrotoluene caused a slight increase in micronucleus formation in peripheral normochromatic erythrocytes in male mice at a high dose level; this finding was not considered conclusive. *o*-Nitrotoluene did not induce micronucleus formation in peripheral normochromatic erythrocytes in female mice or in polychromatic erythrocytes in the bone marrow of male rats or mice (NTP 2002). Following *in vivo* exposure of rats to *o*-nitrotoluene, DNA repair was increased in liver cells isolated from males, but not from females or germ-free males. These results, together with *o*-nitrotoluene's inability to induce DNA repair in hepatocytes *in vitro*, suggest that activation of *o*-nitrotoluene to become genotoxic is sex-specific and depends on both mammalian metabolism and metabolism by intestinal bacteria (Doolittle *et al.* 1983). However, *o*-nitrotoluene also caused tumors in other tissues in rats and mice of both sexes, suggesting that other activation mechanisms exist.

In rats exposed to *o*-nitrotoluene *in vivo*, DNA adducts were detected in the liver of males but not females (NTP 2008). Formation of DNA adducts was consistent with the reaction of intermediate compounds derived from *o*-aminobenzyl alcohol with guanine or adenine bases (Jones *et al.* 2003). The pattern of mutations in oncogenes from *o*-nitrotoluene-induced tumors was also consistent with guanine adduct formation: the majority of *p53* mutations in hemangiosarcomas were G:C to A:T transitions, and almost all the *K-ras* mutations in cecal carcinomas were G:C to T:A transversions (Hong *et al.* 2003, Sills *et al.* 2004). Mutations in the *p53*, *β-catenin*, and *K-ras* genes also were found in hemangiosarcomas from mice exposed to *o*-nitrotoluene, but not in spontaneously occurring hemangiosarcomas from unexposed mice (Hong *et al.* 2003).

In factory workers exposed to *o*-nitrotoluene, *o*-nitrotoluene-hemoglobin adducts were detected in the blood (Jones *et al.* 2005a), and

o-nitrobenzoic acid and *o*-nitrobenzyl alcohol were detected in the urine (Jones *et al.* 2005b), providing evidence that human exposure to *o*-nitrotoluene results in production of a reactive metabolite(s). In addition, adducts between hemoglobin and 2-methylaniline (a metabolite of *o*-nitrotoluene) were identified in both exposed workers and exposed rats, and the level of 2-methylaniline–hemoglobin adducts in the blood of rats was proportional to the level of 2-methylaniline–DNA adducts in the livers of rats (Jones and Sabbioni 2003, Jones *et al.* 2003).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to *o*-nitrotoluene. One cohort study of workers involved in the manufacture of magenta dye mentioned exposure of workers to *o*-nitrotoluene as part of the manufacturing process. A large excess of bladder cancer was reported; however, the workers were also exposed to other chemicals — *o*-toluidine (2-methylaniline) and 4,4'-methylenebis(2-methylaniline)—that are suspected of causing bladder cancer (Rubino *et al.* 1982). Two other studies of magenta manufacturing workers also reported an excess of bladder cancer, but did not report whether the workers were exposed to *o*-nitrotoluene (Case and Pearson 1954, Vineis and Magnani 1985).

Properties

o-Nitrotoluene is a nitroaromatic compound. It is one of three isomers of nitrotoluene; the other two are *m*-nitrotoluene (also known as 3-nitrotoluene) and *p*-nitrotoluene (also known as 4-nitrotoluene). At room temperature, *o*-nitrotoluene is a yellow liquid with an odor of bitter almonds. It is slightly soluble in water and soluble in acetone, benzene, chloroform, diethyl ether, ethanol, and petroleum ether. It has a flash point of 106°C (closed cup) and an autoignition temperature of 305°C (PTCL 2003). It does not ignite easily; however, it may burn, and containers of *o*-nitrotoluene may explode when heated (HSDB 2010). Physical and chemical properties of *o*-nitrotoluene are listed in the following table.

Property	Information
Molecular weight	137.1
Specific gravity	1.162 at 19°C/15°C
Melting point	–9.5°C (needles); –2.9°C (crystals)
Boiling point	222°C at 760 mm Hg
Log K_{ow}	2.30
Water solubility	650 mg/L at 30°C
Vapor pressure (mm Hg)	0.188 at 25°C
Vapor density relative to air	4.73

Source: HSDB 2010.

Use

o-Nitrotoluene is used primarily in the production of *o*-toluidine (also known as *o*-aminotoluene or 2-methylaniline), 2-amino-4-chlorotoluene, 2-amino-6-chlorotoluene, *o*-toluidine-4-sulfonic acid, and other chemicals that are intermediates in the production of various azo dyes (IARC 1996). It is also used in the manufacture of (or the manufacture of intermediates for) other dyes, such as magenta and various sulfur dyes for cotton, wool, silk, leather, and paper (IARC 1996, HSDB 2010). In addition, it is used as an intermediate in the synthesis of (or the synthesis of intermediates for) explosives and a variety of organic chemicals, including compounds used in the agricultural chemical, pesticide, petrochemical, pharmaceutical, and rubber industries (HSDB 2010).

Production

o-Nitrotoluene is produced principally by the nitration of toluene with a mixture of nitric acid and either sulfuric, aromatic sulfonic, or phosphoric acid (IARC 1996). U.S. production of *o*-nitrotoluene was calculated as 13 billion grams (29 million pounds) for 1981 (HSDB 2010) and was estimated at 16,120 metric tons (35.5 million pounds) for 1993 (Dunlap 1998). The U.S. Environmental Protection Agency lists *o*-nitrotoluene as a high-production-volume chemical. In 2010, *o*-nitrotoluene was produced by one U.S. manufacturer (SRI 2010) and was available from 14 U.S. suppliers (ChemSources 2010). No data on U.S. imports or exports of *o*-nitrotoluene were found. Reports filed between 1986 and 2002 under EPA's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of *o*-nitrotoluene totaled 10 million to 50 million pounds (EPA 2004).

Exposure

Exposure to *o*-nitrotoluene in the United States is expected to result primarily from dermal and inhalation exposure during its production and use. The general population may be exposed to *o*-nitrotoluene as a result of its occurrence in the environment from (1) inadvertent spills of *o*-nitrotoluene or chemical mixtures containing *o*-nitrotoluene, (2) emissions directly into the environment, or (3) breakdown products of dinitrotoluenes (DNT) and trinitrotoluenes (TNT). *o*-Nitrotoluene has been detected in U.S. air and water. The National Response Center database contains reports of two spills reported as *o*-nitrotoluene in 1990 and one spill reported as nitrotoluene (*o*-, *p*-, and mixtures) in 2000 (NRC 2008). Two ambient-air samples collected in Boise, Idaho, in the winter of 1986–87 contained *o*-nitrotoluene vapor at concentrations of 0.03 and 0.29 ng/m³ (Nishioka and Lewtas 1992). *o*-Nitrotoluene was also detected in a paper-mill wastewater lagoon (concentration and location not reported) (HSDB 2010) and at concentrations ranging from 320 to 16,000 µg/L in the effluent of a U.S. plant producing TNT (IARC 1996, HSDB 2010).

DNT and TNT are used in the production of commercial and military explosives, and *o*-nitrotoluene has been found in groundwater, private well water, surface water, and soil at or near munitions production facilities and military training grounds. *o*-Nitrotoluene was found at average concentrations of 42.6 mg/L (42,600 µg/L) (Best *et al.* 2001) and 2.9 mg/L (2,900 µg/L) (Spain *et al.* 1999) in groundwater at a Tennessee munitions arsenal. At a facility that has produced munitions since World War II, *o*-nitrotoluene has been detected sporadically during routine groundwater monitoring of both the Ogallala aquifer, at concentrations of 0.12 to 2.9 µg/L (both measured in 2004), and a perched aquifer above the Ogallala, at concentrations of 0.14 µg/L (in 2003) to 5 µg/L (in 2004) (Pantex 2008). At a former munitions production site in Wisconsin, *o*-nitrotoluene was detected in off-site private well water at concentrations of up to 0.095 µg/L (WDHFS 2002). At a historical testing ground in Idaho, soil contaminated with TNT at a concentration of 39,100 ppm contained *o*-nitrotoluene at a concentration of 1.4 ppm (Radtke *et al.* 2002).

No information was found on the number of U.S. workers potentially exposed to *o*-nitrotoluene in the production of chemical intermediates. *o*-Nitrotoluene was detected at a concentration of 47 ng/m³ in ambient air at a chemical manufacturing plant in New Jersey (IARC 1996) and at air concentrations of up to 2.0 mg/m³ in the nitrotoluene production area of a Swedish plant producing pharmaceuticals and explosives (Ahlborg *et al.* 1985). The American Conference of Governmental Industrial Hygienists considers *o*-nitrotoluene to be an inducer of methemoglobin and recommends that methemoglo-

bin in blood be used as a biological exposure index for *o*-nitrotoluene (and the other nitrotoluene isomers) (ACGIH 2009).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for the safe transport of *o*-nitrotoluene on barges.

Department of Transportation (DOT)

o-Nitrotoluene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Safety measures after spills or leaks are prescribed in accordance with *o*-nitrotoluene being a combustible toxic hazardous material.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

(EPA has not carried out an Integrated Risk Information System assessment for *o*-nitrotoluene.)

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 5 ppm (30 mg/m³).

Potential for dermal absorption; skin exposure should be prevented as necessary through the use of good work practices and gloves, coveralls, goggles, and other appropriate equipment.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

Potential for dermal absorption.

Biological Exposure Index (BEI): Methemoglobin in blood not to exceed 1.5% of hemoglobin measured during or at the end of a shift.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 200 ppm.

Recommended exposure limit (REL) = 2 ppm (11 mg/m³).

Potential for dermal absorption.

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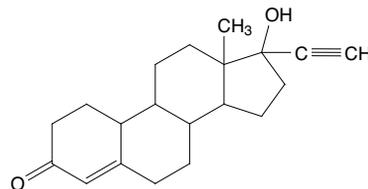
Norethisterone

CAS No. 68-22-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as norethindrone



Carcinogenicity

Norethisterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Norethisterone caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Oral ex-

posure to norethisterone caused benign liver tumors (hepatocellular neoplasia) in male mice and male rats, pituitary-gland tumors in female mice, and benign and malignant mammary-gland tumors in male rats. Subcutaneous implantation of pellets containing norethisterone caused ovarian tumors (granulosa-cell neoplasia) in female mice (IARC 1974, 1979). Norethisterone acetate administered orally caused benign liver tumors in male mice and female rats and uterine polyps in female rats (IARC 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to norethisterone.

Studies on Mechanisms of Carcinogenesis

In female rats orally exposed first to the carcinogen *N*-2-acetylaminofluorene at a non-tumorigenic dose and then to norethisterone, benign and malignant liver tumors (neoplastic nodules and hepatocellular carcinoma) were observed (IARC 1982).

Joint dietary administration of norethisterone and synthetic estrogens to rodents caused tumors at the same tissue sites as observed for norethisterone alone. Pituitary-gland tumors were observed in mice of both sexes following administration of norethisterone plus mestranol or ethinylestradiol and also following administration of norethisterone acetate plus ethinylestradiol (an effect not seen in mice administered norethisterone acetate alone). In rats, administration of norethisterone plus mestranol caused malignant mammary-gland tumors in both sexes and benign liver tumors in males, and administration of norethisterone acetate plus ethinylestradiol caused benign mammary-gland and liver tumors in both sexes.

Properties

Norethisterone is a synthetic steroidal progestin that is a white crystalline powder at room temperature (IARC 1974, HSDB 2009). It is slightly soluble in 95% ethanol, pyridine, acetone, chloroform, dioxane, vegetable oil, and diethyl ether and sparingly soluble in alcohol. It is stable in air, but unstable in air in the presence of light (Akron 2009). When heated to decomposition, it emits acrid smoke and fumes. Physical and chemical properties of norethisterone are listed in the following table.

Property	Information
Molecular weight	298.4 ^a
Density	1.2 g/cm ^{3b}
Melting point	203°C to 204°C ^a
Log <i>K</i> _{ow}	2.97 ^a
Water solubility	0.00704 g/L at 25°C ^a
Vapor pressure	7.31 × 10 ⁻⁹ mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Norethisterone, an orally active progestin hormone, has been used in small amounts in human medicine since 1957 to treat conditions such as amenorrhea, dysfunctional uterine bleeding, endometriosis, premenstrual tension, and dysmenorrhea, and in hormone replacement therapies (IARC 1979, MedlinePlus 2009b). Since 1962, the most common use in the United States has been as the progestin in progestin-estrogen combination oral contraceptives. Norethisterone is also used as an intermediate in the commercial synthesis of norethisterone acetate and possibly in the synthesis of ethynodiol diacetate (IARC 1974). Norethisterone acetate has been used in the treatment of inoperable breast cancer or as an adjunct to surgery or radiotherapy (IARC 1979).

Production

Total annual U.S. sales of human medicine containing norethisterone before 1972 were estimated at less than 4,400 lb (IARC 1974). In 2009, norethisterone was produced by one manufacturer each in the United States, Europe, and India (SRI 2009) and was available from 22 suppliers, including 11 U.S. suppliers (ChemSources 2009). No data on U.S. imports of norethisterone were found.

Exposure

The routes of potential human exposure to norethisterone are ingestion, dermal contact, and inhalation (HSDB 2009). Norethisterone is a synthetic hormone and is administered most often as a contraceptive or hormone replacement in oral tablets or dermal patches (MedlinePlus 2009a). In 2009, 59 prescription products registered with the U.S. Food and Drug Administration contained norethindrone or norethindrone acetate as an active ingredient, of which 2 were dermal patches and 57 were oral tablets. Both dermal patches contained norethindrone acetate. When used as an oral contraceptive, norethisterone usually is given at a dose of 0.5 to 2.0 mg daily in combination with mestranol or ethinylestradiol (synthetic estrogen hormones) (IARC 1979). In the contraceptive "mini-pill," it is used continuously at a daily dose of 0.35 mg. Norethisterone acetate is also administered in several hormone replacement therapies (Medline Plus 2009b). For other medicinal uses, daily doses of norethisterone range from 10 to 30 mg (IARC 1979).

A study conducted to determine the presence of hormones in environmental water samples detected norethisterone in 12.8% of U.S. stream water samples, at a median concentration of 0.048 µg/L (Kolpin *et al.* 2002), but not in any sample collected in the Czech Republic (Morteani *et al.* 2006).

Potential occupational exposure to norethisterone may occur through inhalation or dermal contact by workers involved in its manufacture, formulation, packaging, or administration (HSDB 2009). In a study conducted in a factory that produced oral contraceptives, norethisterone was found in various sectors of the working environment at concentrations ranging from 0.30 to 59.56 µg/m³ in airborne dust and from 0.019 to 14.7 µg/cm² in wipe samples (IARC 1979).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Norethisterone is regulated as a prescription drug and is subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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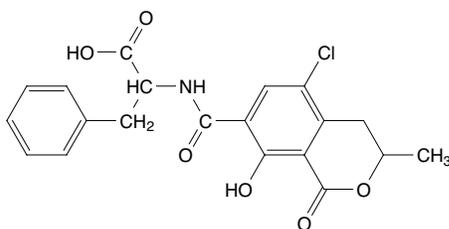
SRI. 2009. *Directory of Chemical Producers*. Menlo Park, CA: SRI Consulting. Database edition. Last accessed: 6/4/09.

Ochratoxin A

CAS No. 303-47-9

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)



Carcinogenicity

Ochratoxin A is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to ochratoxin A caused tumors at several different tissue sites in mice and rats. Dietary administration of ochratoxin A caused benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and benign and malignant kidney tumors (renal-cell adenoma and carcinoma) in male mice (IARC 1983, 1987). When administered by stomach tube, ochratoxin A caused benign and/or metastatic malignant kidney tumors (renal-cell adenoma or carcinoma) in rats of both sexes and benign mammary-gland tumors (fibroadenoma) in female rats (NTP 1989, Huff 1991). Since ochratoxin A was listed in the *Sixth Annual Report on Carcinogens*, an additional study in male rats has been identified, which also found an increased incidence of kidney tumors following dietary exposure to ochratoxin A (Mantle *et al.* 2005).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to ochratoxin A. In descriptive ecological studies, a relatively high frequency of contamination of cereals and beans with ochratoxin A has been reported in an area of Yugoslavia where a potentially fatal chronic renal disease, Balkan endemic nephropathy (BEN),

is present (IARC 1983, 1987). The geographical distribution of this disease has been linked, in turn, to areas of increased incidence and mortality from urinary-tract tumors.

Since ochratoxin A was listed in the *Sixth Annual Report on Carcinogens*, additional studies in humans have been identified; however, the findings concerning a relationship between exposure to ochratoxin A and cancer are mixed. Ecological studies have found correlations between the geographic distribution of urinary-tract tumors and exposure to ochratoxin A (Pfohl-Leszkowicz *et al.* 2002, Clark and Snedeker 2006). In addition, higher blood levels of ochratoxin A were observed in individuals with BEN or urinary-tract tumors than in unaffected residents of the same areas (Petkova-Bocharova and Castegnaro 1991), and levels of ochratoxin A were higher in a small sample of Egyptian patients with urinary-tract tumors than among healthy control subjects (Wafa *et al.* 1998). However, the International Agency for Research on Cancer reported that there was no clear association between ochratoxin A-contaminated foods and BEN in Bulgaria (IARC 1993), and a small study of urinary-bladder cancer in Pakistan found no differences in blood ochratoxin A concentrations between case and control subjects (Aslam *et al.* 2006). Exposure to aristolochic acid, which also correlates with the geographical distribution of urinary-tract tumors, has been proposed as a risk factor for BEN and the associated urinary-tract tumors (Grollman *et al.* 2007).

Properties

Ochratoxin A is a naturally occurring fungal toxin that occurs as a colorless crystal at room temperature under normal light, but exhibits green and blue fluorescence in ultraviolet light (IARC 1976). The free acid is insoluble in water but is moderately soluble in organic solvents such as chloroform, ethanol, methanol, and xylene (Akron 2010, HSDB 2010). It is unstable in light, especially in very humid conditions; however, it is stable in the dark in ethanol solutions (Akron 2010). Ochratoxin A is also fairly stable to heat; in cereal products, up to 35% of the toxin survives autoclaving for up to 3 hours (IARC 1976). Physical and chemical properties of ochratoxin A are listed in the following table.

Property	Information
Molecular weight	403.8 ^a
Density	1.366 g/mL ^b
Melting point	169°C ^a
Log K_{ow}	4.74 ^a
Water solubility	1.31 mg/L at 25°C ^c
Vapor pressure	7.56×10^{-15} mm Hg at 25°C ^c
Dissociation constant (pK_a)	3.46 ^b

Sources: ^aHSDB 2010, ^bAkron 2010, ^cSR 2010.

Use

Ochratoxin A has no known commercial use. It has been used as a research chemical (HSDB 2010).

Production

Ochratoxin A is a naturally occurring mycotoxin (IARC 1976). The most important ochratoxin A-producing species is *Aspergillus ochraceus* (IARC 1993). Ochratoxin A is also produced by one species of *Penicillium*, *P. verrucosum*, and by rare species in the *A. ochraceus* group. Ochratoxin A is not produced commercially (IARC 1983); however, in 2010, it was available from 16 suppliers worldwide, including 8 U.S. suppliers (ChemSources 2010).

Exposure

The widespread occurrence of ochratoxin A in food and animal feed results in probable human exposure (IARC 1976, 1993). Ochratoxin A

is formed by *Penicillium* in colder climates and by *Aspergillus* in tropical and subtropical regions. It is found on corn, peanuts, storage grains, cottonseed, and decaying vegetation (Merck 1996). It has been detected in peanuts, coffee beans, bread, flour, rice, peas, and beans and in moldy cereals, including wheat, maize, rye, barley, and oats (IARC 1983, 1993). Concentrations in cereals ranged from 0.03 to 27.5 ppm (Scott *et al.* 1972, Krogh *et al.* 1973).

Ochratoxin A has been detected in fresh grapes, grape juice, dried vine fruits, musts, and all types of wine throughout the world. It was found in Cabernet Sauvignon grapes from Portugal at a concentration of 115.6 µg/kg (Serra *et al.* 2006), in grape juice at 0.337 µg/kg (Clark and Snedeker 2006), and in dried fruit (raisins, currants, and sultanas) purchased in the United Kingdom at concentrations of up to 53.6 µg/kg (Rizzo *et al.* 2002). Concentrations are higher in red wines than in rosé wines, and higher in rosé wines than in wines or special wines (e.g., Marsala).

Ochratoxin A has been detected in coffee throughout the world in all stages of production, from coffee cherries to brewed coffee. It was found in coffee cherries and beans in Brazil at concentrations of up to 3.3 µg/kg (Clark and Snedeker 2006). The highest concentration found in green (processed) coffee was 56 µg/kg in coffee from the Ivory Coast (Studer-Rohr *et al.* 1995). Ochratoxin A was also found in roasted coffee from Ethiopia at 2.0 µg/kg (Napolitano *et al.* 2007) and instant coffee from Brazil at 6.29 µg/kg (De Almeida *et al.* 2007). The highest concentration found in brewed coffee was 4.2 µg/L, measured in Switzerland (Studer-Rohr *et al.* 1995). Ochratoxin A has also been detected in cocoa in all stages of production, from raw beans to chocolate and chocolate cream, in the tropical areas where cocoa is produced. The highest concentration found at any stage of cocoa production was 48.02 µg/kg in wounded cocoa beans in Cameroon (Mounjouenpou *et al.* 2008). The worldwide mean concentration in cocoa cake was 2.79 µg/kg, the mean concentration in cocoa powder in Africa was 2.41 µg/kg, and the worldwide mean concentration in chocolate and chocolate cream was 0.63 µg/kg (Bonvehi 2004).

Ochratoxin A has been detected in spices and licorice flavoring and candy in many countries where these spices and flavorings are important in the diet. Although ochratoxin A from contaminated barley can occur in beer, a survey of all U.S. breweries (130 at the time) did not detect ochratoxin A in beer or malted barley (detection limit = 10 µg/kg). In moderately contaminated barley, the malting process completely degrades ochratoxin A; however, 2% to 7% of the toxin remained in the final product from heavily contaminated barley (IARC 1983). Residues of ochratoxin A were detected in samples of meat from animals slaughtered immediately after consuming contaminated feed; concentrations of 10 to 920 µg/kg were found in sausage, ham, and bacon (Krogh *et al.* 1977, IARC 1983, 1993). Ochratoxin A also was found in peas and beans from Sweden at 442 µg/kg, peanut seeds from Argentina at up to 170 µg/kg, and olives from Greece at 1.86 µg/kg (Clark and Snedeker 2006, Ghitakou *et al.* 2006, Magnoli *et al.* 2006).

In ambient air, ochratoxin A exists completely in the particulate phase (HSDB 2010). It is immobile in soil. Ochratoxin A has been measured in airborne particulates in mainly occupational settings where contaminated items were stored or processed. Where black pepper was processed, the maximum ochratoxin A concentrations were 0.43 ng/m³ in ambient air and in 8.304 ng/m³ personal air samples (Brera *et al.* 2002). Lower concentrations were found in ambient air and personal air monitors in workplaces where cocoa, coffee, and nutmeg were handled (Brera *et al.* 2002, Iavicoli *et al.* 2002). Ochratoxin A has also been measured in settled dust collected in residential and agricultural locations. The highest concentration was 1,581.8 µg/kg in dust in an air supply duct in a U.S. residence; other

dust samples from the same residence all had high levels of ochratoxin A (Richard *et al.* 1999).

Ochratoxin A has been measured in the blood and urine of exposed individuals around the world. The concentrations are exceptionally high in Bulgaria, where BEN occurs. Concentrations of ochratoxin A in the blood have been measured at up to 100 ng/mL (100 µg/L) in Bulgaria (Clark and Snedeker 2006) and up to 66.2 µg/L in Tunisia (Abid *et al.* 2003). Urinary concentrations have been measured at up to 148 µg/L for girls in Sierra Leone (Jonsyn-Ellis 2000) and 0.604 µg/L for individuals with BEN in Bulgaria (Castegnaro *et al.* 1991). The highest concentration in breast milk was 1,890 ng/L in Egypt (Hassan *et al.* 2006). Total daily intake of ochratoxin A varies among countries, depending on food-handling methods, and has been estimated based on total diets or on consumption of specific contaminated foods or beverages. The highest estimated daily intake was 1.21 µg for adults with BEN in Bulgaria (Clark and Snedeker 2006), and the highest estimated daily intake for children was 3.6 ng/kg of body weight for Swiss children who consumed grape juice.

Regulations

No specific regulations or guidelines relevant to reduction of exposure to ochratoxin A were identified.

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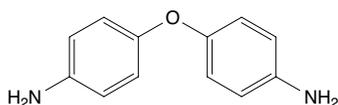
4,4'-Oxydianiline

CAS No. 101-80-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as 4,4'-diaminodiphenyl ether



Carcinogenicity

4,4'-Oxydianiline is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

4,4'-Oxydianiline caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Dietary administration of 4,4'-oxydianiline increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice and rats of both sexes. It also increased the combined incidence of benign and malignant thyroid-gland tumors (follicular-cell adenoma or carcinoma) in rats of both sexes and caused benign thyroid-gland tumors (follicular-cell adenoma) in female mice and benign Harderian-gland tumors (adenoma) in mice of both sexes (IARC 1978, 1982, NCI 1980). Subcutaneous injection of 4,4'-oxydianiline increased the combined incidence of benign and malignant liver tumors (hepatocellular neoplasia) in rats of both sexes (IARC 1978, 1982).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-oxydianiline.

Properties

4,4'-Oxydianiline is an aromatic diamine ether that is a colorless crystal at room temperature (IARC 1982). It is insoluble in water, benzene, carbon tetrachloride, and ethanol, but it is soluble in acetone. 4,4'-Oxydianiline is stable under normal conditions. However, it is combustible, hygroscopic, and incompatible with strong oxidizing agents (Columbia 2009). Physical and chemical properties of 4,4'-oxydianiline are listed in the following table.

Property	Information
Molecular weight	200.3 ^a
Melting point	186°C to 187°C ^a
Boiling point	> 300°C ^a
Log K_{ow}	2.06 ^a
Water solubility	0.560 g/L at 25°C ^b
Vapor pressure	4.36×10^{-6} mm Hg at 25°C ^b
Dissociation constant (pK_a)	8.52 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

4,4'-Oxydianiline is used primarily in the production of polyimide and poly(ester)imide resins. These resins are used in the manufacture of temperature-resistant products such as wire enamels, electrical equipment, coated fabrics, flame-retardant fibers, oil sealants and retainers, binders in laminates for printed circuits and honeycomb structures, molding of grinding wheels, and polymers used as adhesives in metal-to-metal bonding of airplane parts (NCI 1980, IARC 1982).

Production

4,4'-Oxydianiline has been commercially produced in the United States since 1959 (IARC 1982). Production was estimated at 100,000 lb to 1 million pounds in 1974 (NCI 1980) and probably over 2,000 lb in 1976 and 1978 (HSDB 2009). The U.S. Environmental Protection Agency's Toxic Substances Control Act (TSCA) Chemical Substance Inventory listed four manufacturers producing a total of about 2,000 lb of 4,4'-oxydianiline in 1977 (EPA 1979). According to the U.S. International Trade Commission, 4,4'-oxydianiline was pro-

duced in undisclosed amounts by three U.S. companies in 1980 and one U.S. company from 1981 to 1988 (USITC 1981, 1989). In 2009, 4,4'-oxydianiline was produced by six manufacturers worldwide, including U.S. manufacturer (SRI 2009), and was available from 32 suppliers, including 18 U.S. suppliers (ChemSources 2009). Reports filed in 1986, 1990, 1998, and 2002 under EPA's TSCA Inventory Update Rule indicated that U.S. production plus imports of 4,4'-oxydianiline totaled 1 million to 10 million pounds; in 1994, inventories dipped to between 10,000 and 500,000 lb (EPA 2004). In 1980, U.S. imports of 4,4'-oxydianiline totaled 48,500 lb (IARC 1982).

Exposure

The routes of potential human exposure to 4,4'-oxydianiline are inhalation and dermal contact. 4,4'-Oxydianiline may be released in waste streams from its production and its use in formulating polyimides (HSDB 2009). In air, it is expected to degrade rapidly (with an estimated half-life of 1.8 hours) by reacting with photochemically produced hydroxyl radicals. The particulate phase is removed via deposition. In soil, 4,4'-oxydianiline undergoes covalent chemical bonding with humic material; moderate leaching is expected in the absence of covalent binding. Since 1988, reported total environmental releases of 4,4'-oxydianiline have remained between 251 and 3,327 lb except in 2002, when 14,663 lb was released, including over 14,000 lb to on-site landfills (TRI 2009). In 2007, three facilities released 2,708 lb of 4,4'-oxydianiline, of which 2,149 lb was released to hazardous-waste landfills, 346 lb to air, and 214 lb to surface water.

Occupational exposure is most likely to occur during the manufacture of 4,4'-oxydianiline or its use in production of polyimide-type resins (HSDB 2009). Exposure may occur through inhalation of dust or through eye or skin contact. The National Occupational Hazard Survey (conducted from 1972 to 1974), estimated that 45 workers potentially were exposed to 4,4'-oxydianiline (NIOSH, 1976). No more recent estimates of occupational exposure were found.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

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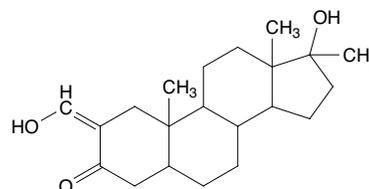
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Oxymetholone

CAS No. 434-07-1

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Oxymetholone is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans.

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of oxymetholone in humans. In numerous case reports, liver tumors have been reported in patients with aplastic anemia, Fanconi's anemia, paroxysmal nocturnal hemoglobinuria, or other disorders who were treated, usually for long periods, with oxymetholone alone or in combination with other androgenic drugs; however, a causal relationship cannot be firmly established (IARC 1977).

Since oxymetholone was listed in the *First Annual Report on Carcinogens*, additional case reports, primarily of liver cancer, have been identified. Some of the reports were of patients with Fanconi's anemia who developed leukemia, liver cancer, or esophageal cancer following oxymetholone treatment (IARC 1987, Linares *et al.* 1991); Fanconi's anemia patients are at increased risk for acute myeloid leukemia and squamous-cell carcinoma of the head, neck, and anogenital regions (Auerbach 2009). Case reports of liver cancer and one report of bile-duct cancer (ampullary carcinoma) also have been reported in patients undergoing oxymetholone treatment for other conditions (Kosaka *et al.* 1996, Nakao *et al.* 2000, Fujino *et al.* 2001, Socas *et al.* 2005).

Cancer Studies in Experimental Animals

No adequate studies in experimental animals were available at the time oxymetholone was listed in the *First Annual Report on Carcinogens*. Since then, a cancer study in rats has been identified. Administration of oxymetholone by stomach tube increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in female rats. Benign lung tumors and benign and malignant skin tumors in female rats also were considered to be related to oxymetholone exposure (NTP 1999)

Properties

Oxymetholone is a synthetic anabolic steroid that is structurally related to the male hormone testosterone (IARC 1977, NTP 1999). It exists at room temperature as white-to-creamy crystals (Akron 2009, NTP 1999). It is practically insoluble in water, but it is soluble in ethanol, dioxane, and ether and very soluble in chloroform (HSDB 2009).

It is sensitive to light (Akron 2009). Physical and chemical properties of oxymetholone are listed in the following table.

Property	Information
Molecular weight	332.5 ^a
Melting point	178°C to 180°C ^a
Log K_{ow}	3.61 ^b
Water solubility	5.21 mg/L at 25°C ^a
Vapor pressure	5.1×10^{-11} mm Hg at 25°C ^a
Dissociation constant (pK_a)	4.5 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Oxymetholone and other synthetic androgens are used to treat a variety of conditions, including hypogonadism and delayed puberty. Androgens are also used to correct hereditary angioneurotic edema, manage breast cancer, promote a positive nitrogen balance following injury or surgery, and stimulate production of red blood cells. Considerable amounts of androgens are consumed by athletes in attempts to improve athletic performance. Oxymetholone is used to promote weight gain and counteract weakness and emaciation resulting from debilitating diseases, such as advanced HIV infection, and after serious infections, burns, trauma, or surgery. It is marketed as a human prescription drug for the treatment of anemia caused by deficient red-blood-cell production. It has also been used in veterinary medicine as an anabolic steroid for small animals. In 1972, the U.S. Food and Drug Administration permitted the use of oxymetholone to treat pituitary dwarfism and as an adjunctive therapy in osteoporosis pending further investigation (NTP 1999). The FDA withdrew its approval for use of oxymetholone in the treatment of pituitary dwarfism in 1980 and in topically applied drug products for over-the-counter use in 1993 (FDA 2010). In 1983, the FDA allowed the continued use of oxymetholone for treatment of "certain anemias" (NTP 1999).

Production

There is no evidence that oxymetholone has ever been produced commercially in the United States (IARC 1977). In 2009, no producers of oxymetholone were identified worldwide (SRI 2009), but it was available from 14 suppliers, including 8 U.S. suppliers (ChemSources 2009). In 1977, U.S. sales of oxymetholone for use in human medicine were estimated to be less than 44 lb annually (IARC 1977). No data on U.S. exports or imports were found specifically for oxymetholone. U.S. imports of all "anabolic agents and androgens" were 35,000 lb in 2000, but no data on U.S. imports or exports in this category since 2001 were found (USITC 2009).

Exposure

The primary routes of potential human exposure to oxymetholone are ingestion and dermal contact (FDA 2009, HSDB 2009). Oxymetholone is administered to children and adults at dosages of 1 to 5 mg/kg of body weight per day for treatment of anemia caused by deficient red-blood-cell production (Pavlatos *et al.* 2001). A regimen of 100 mg twice a day is recommended as an effective dose for HIV wasting (Hengge *et al.* 2003).

Since the 1950s, increasing numbers of athletes have used anabolic steroid drugs in efforts to increase strength (NTP 1999). In the 1980s, it was estimated that 80% to 100% of national and international male bodybuilders, weightlifters, and participants in the shot put, discus, hammer, and javelin throws used anabolic steroids; football players and competitors in other sports used anabolic steroids to a lesser extent. It has been estimated that more than 1 million individuals abuse steroids in the United States (Hall and Hall 2005). Most abusers start using steroids by age 16. It has been reported that between 4% and

12% of male high-school students and 0.5% to 2.5% of female high-school students abuse steroids (Riem and Hursey 1995). Dosages used by athletes are often much higher than the normal endogenous testosterone production of 4 to 10 mg per day. Documented daily dosages range from 10 or 15 to 300 mg, with anecdotal reports of up to 2 g. Internet sites that sell anabolic steroids state that male athletes typically take oxymetholone at daily dosages of 50 to 150 mg (Zupplements 2010). Generally, a variety of injectable and oral steroids are taken at dosages that increase, peak, and then taper off prior to competitions and potential drug tests (NTP 1999).

Health professionals such as pharmacists, physicians, and nurses may potentially be exposed while dispensing or administering drug products containing oxymetholone. The risk of occupational exposure during production is low, since the oxymetholone is not produced in the United States (HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 742 workers, including 359 women, potentially were exposed to oxymetholone (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Oxymetholone is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Phenacetin and Analgesic Mixtures Containing Phenacetin

Introduction

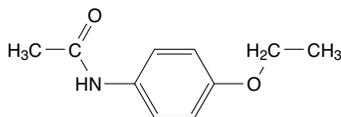
Phenacetin was first listed in the *First Annual Report on Carcinogens* (1980), as *reasonably anticipated to be a human carcinogen*, and analgesic mixtures containing phenacetin were first listed in the *Fourth Annual Report on Carcinogens* (1985), as *known to be human carcinogens*. The evidence for the carcinogenicity of these two substances is discussed separately; however, information on properties, use, production, exposure, and regulations is common to both and is combined into one section following the discussion of carcinogenicity.

Phenacetin

CAS No. 62-44-2

Reasonably anticipated to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Phenacetin is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary administration of phenacetin caused benign and malignant tumors of the urinary tract in mice and rats of both sexes and of the nasal cavity (adenocarcinoma, squamous-cell carcinoma, and transitional-cell carcinoma) in rats of both sexes (Isaka *et al.* 1979, IARC 1980).

Cancer Studies in Humans

There is limited evidence for the carcinogenicity of phenacetin in humans. There are numerous case reports of kidney cancer (transitional-

cell carcinoma of the renal pelvis) among patients who had consumed large amounts of analgesic mixtures containing phenacetin; however, it is not possible to specify which component(s) of the mixture is carcinogenic (IARC 1977, 1980).

Analgesic Mixtures Containing Phenacetin

CAS No.: none assigned

Known to be human carcinogens

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Carcinogenicity

Analgesic mixtures containing phenacetin are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Many cases of kidney and urinary-tract cancer have been reported in patients who had consumed large amounts of analgesic mixtures containing phenacetin. Case-control studies have consistently shown a relationship between cancer of the renal pelvis and urinary bladder and use of phenacetin-containing analgesics that is not explained by confounding by other causes of cancer. A dose-response relationship was observed in some studies (IARC 1977, 1982, 1987).

Cancer Studies in Experimental Animals

There is limited evidence for the carcinogenicity of analgesic mixtures containing phenacetin from studies in experimental animals. In male rats, oral exposure to a mixture of phenacetin, phenazone, and caffeine caused liver cancer (hepatocellular carcinoma), and phenacetin alone or in combination with phenazone slightly increased the incidence of kidney tumors (renal-cell and renal-pelvis tumors) (Johansson 1981, IARC 1982).

Phenacetin and Analgesic Mixtures Containing Phenacetin

Properties

Phenacetin occurs at room temperature as white, odorless monoclinic prisms. It is soluble in water (more so in hot than cold water), alcohol, glycerol, and acetone and is slightly soluble in benzene. It is unstable to oxidizing agents, iodine, and nitrating agents (IARC 1977). Physical and chemical properties of phenacetin are listed in the following table.

Property	Information
Molecular weight	179.2
Melting point	134°C to 135°C
Log K_{ow}	1.58
Water solubility	30 mg/L at 25°C
Vapor pressure	0.00316 mm Hg at 25°C

Source: HSDB 2009.

Use

Phenacetin was used as an analgesic and fever-reducing drug in both human and veterinary medicine for many years. It was introduced into therapy in 1887 and was extensively used in analgesic mixtures until it was implicated in kidney disease (nephropathy) due to abuse of analgesics (Flower *et al.* 1985) and was withdrawn from the U.S. market in 1983 (Ronco and Flahault 1994; FDA 1998, 1999). Phenacetin also was previously used as a stabilizer for hydrogen peroxide in hair-bleaching preparations (IARC 1980, HSDB 2009).

Production

Phenacetin was first produced in the United States in the 1920s and was used in human medicine until it was banned in the early 1980s (IARC 1977, FDA 1999). Total annual sales of phenacetin for medical use were estimated to be less than 640,000 kg (1.4 million pounds) by the late 1970s. Phenacetin was produced by one U.S. company in 1974 and two U.S. companies in 1978. In 2009, phenacetin was produced by two manufacturers worldwide (one each in Europe and Mexico) (SRI 2009) and was available from 32 suppliers, including 21 U.S. suppliers (ChemSources 2009). U.S. imports of phenacetin were 67,000 kg (148,000 lb) in 1972, 94,000 kg (207,000 lb) in 1973, 192,000 kg (423,000 lb) in 1974, 232,000 kg (511,000 lb) in 1976, 282,000 kg (620,000 lb) in 1978, and 37,500 kg (83,000 lb) in 1984 (IARC 1977, 1980, HSDB 2009). No more recent data on U.S. imports or exports were found. Reports filed in 1994, 1998, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of phenacetin totaled less than 10,000 lb (EPA 2004); no earlier or more recent reports were filed.

Analgesic mixtures containing phenacetin were produced until phenacetin was removed from the market in the early 1980s. No specific U.S. historical production, import, or export data were found for the analgesic mixtures.

Exposure

Phenacetin and analgesic mixtures containing phenacetin were administered in tablet and capsule form. Until 1983, phenacetin was used in over-the-counter remedies for pain and fever; however, it no longer is used in drug products in the United States. The usual dosage was 300 mg four to six times per day, and the daily dose was not to exceed 2 g (IARC 1977). No information was found regarding the number of people who used phenacetin or analgesic mixtures containing phenacetin before it was withdrawn from the U.S. market, and no estimate of current exposure was found. In the past, occupational exposure may have occurred through inhalation or dermal contact by workers involved in the manufacture, formulation, packaging, or administration of phenacetin. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 18,808 workers potentially were exposed to phenacetin and 869 workers potentially were exposed to phenacetin powder (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of phenacetin = U187.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Phenacetin may not be used in over-the-counter drugs for digestive aid, for weight control, as an orally administered menstrual drug product, or as an internal analgesic.

Phenacetin has been withdrawn from the market because it was found to be unsafe or not effective, and it may not be compounded.

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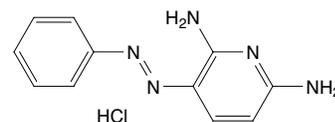
Phenazopyridine Hydrochloride

CAS No. 136-40-3

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as Pyridium (a registered trademark of Warner Chilcott)



Carcinogenicity

Phenazopyridine hydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to phenazopyridine hydrochloride caused tumors in two rodent species and at two different tissue sites. In female mice, it caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma). In rats of both sexes, it caused benign or malignant colorectal tumors (adenoma, adenocarcinoma, or sarcoma) (NCI 1978).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to phenazopyridine hydrochloride.

Properties

Phenazopyridine hydrochloride is a heterocyclic aromatic azo compound that exists at room temperature as brick-red microcrystals with a slight violet luster (Akron 2009). It is slightly soluble in cold water,

ethanol, and lanolin; soluble in boiling water, acetic acid, glycerol, ethylene glycol, and propylene glycol; and insoluble in acetone, benzene, chloroform, diethyl ether, and toluene (IARC 1975). Physical and chemical properties of phenazopyridine hydrochloride are listed in the following table.

Property	Information
Molecular weight	249.7 ^a
Melting point	235°C ^a
Log K_{ow}	-0.30 ^b
Water solubility	15.9 g/L at 25°C ^b
Vapor pressure	3.51×10^{-11} mm Hg at 25°C ^b

Sources: ^aIARC 1975, ^bChemIDplus 2009.

Use

Phenazopyridine hydrochloride is used as an analgesic drug to reduce pain, burning, and discomfort associated with urinary tract infections or irritation. It has frequently been used in combination with sulfonamides and antibiotics (IARC 1975, 1980, HSDB 2009, Medline Plus 2009).

Production

Commercial production of phenazopyridine hydrochloride in the United States began in 1944. In the early 1970s, it was produced by two companies (IARC 1975). In 1979, estimated annual North American production was 22,000 to 110,000 lb (IARC 1980). In 2009, phenazopyridine hydrochloride was produced by seven manufacturers worldwide, including two U.S. manufacturers (SRI 2009), and was available from 21 suppliers, including 12 U.S. suppliers (ChemSources 2009). In 1978, U.S. imports of phenazopyridine hydrochloride totaled 15,400 lb (IARC 1980). No more recent data on U.S. production, imports, or exports were found.

Exposure

Exposure to phenazopyridine hydrochloride may occur through its ingestion as a drug or through dermal contact or inhalation of dust during its production, formulation, packaging, or administration (HSDB 2009, MedlinePlus 2009). Phenazopyridine hydrochloride has been marketed both as a prescription drug and as an over-the-counter product (FDA 2003). Oral tablets containing phenazopyridine hydrochloride in combination either with sulfamethoxazole, sulfamethoxazole and trimethoprim or with sulfisoxazole previously were available by prescription (FDA 2009). In 2010, about a dozen brands of over-the-counter products containing phenazopyridine were available (Drugs.com 2010). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,546 workers, including 1,328 women, potentially were exposed to phenazopyridine hydrochloride (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

As a prescription drug, phenazopyridine hydrochloride is subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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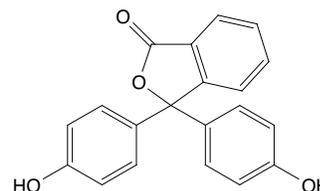
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Phenolphthalein

CAS No. 77-09-8

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Phenolphthalein is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to phenolphthalein caused tumors at several different tissue sites in mice and rats. Dietary administration of phenolphthalein caused thymic lymphoma and connective-tissue tumors (histiocytic sarcoma at various tissue sites) in mice of both sexes. It also increased the combined incidence of all types of malignant lymphoma in female mice and caused benign tumors of the ovary (sex-cord-stromal tumors) in female mice, the adrenal gland (pheochromocytoma of the adrenal medulla) in rats of both sexes, and the kidney (renal-cell adenoma) in male rats (NTP 1996).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to phenolphthalein. In several case-control studies of the

risk of colon cancer or adenomatous colorectal polyps and the use of phenolphthalein-containing laxatives, the results were inconsistent. Most of the studies had limited statistical power (IARC 2000). Since phenolphthalein was listed in *Ninth Report on Carcinogens*, additional epidemiological studies have been identified. Two small case-control studies found no significant association between epithelial ovarian cancer and the use of phenolphthalein as a laxative (Cooper *et al.* 2000, 2004). A case-control study of cancer at several tissue sites reported a statistically nonsignificant twofold increase in the risk of colon cancer among heavy users of phenolphthalein; however, the study was limited by small numbers of cases for most tumor sites in subjects with higher exposure (Coogan *et al.* 2000).

Studies on Mechanisms of Carcinogenesis

Phenolphthalein caused genetic damage in several *in vitro* and *in vivo* mammalian test systems. It caused *hprt* gene mutations, chromosomal aberrations, and morphological transformation in Syrian hamster embryo cells with or without mammalian metabolic activation, and it caused chromosomal aberrations in Chinese hamster ovary cells with metabolic activation. *In vivo*, phenolphthalein caused micronucleus formation in mouse erythrocytes after repeated, but not single, exposure by gavage or in the diet, and dietary administration for 13 weeks caused abnormal sperm in male mice (NTP 1999, IARC 2000). Dietary administration of phenolphthalein to female heterozygous *p53*-deficient transgenic mice for 26 weeks caused micronucleus formation and malignant thymic lymphoma. In the tumors, the normal allele of the *p53* tumor-suppressor gene had been lost, suggesting the involvement of a mutagenic mechanism in tumor induction and/or progression (Dunnick *et al.* 1997).

Phenolphthalein is absorbed from the gastrointestinal tract and undergoes extensive first-pass metabolism in the intestinal epithelium and liver, resulting in almost complete conversion to its glucuronide, which is eliminated in the bile (NTP 1999). Phenolphthalein enhances the production of oxygen radicals in *in vitro* systems (IARC 2000). *In vivo*, reduction of phenoxyl radicals could allow re-formation of phenolphthalein, establishing a futile cycle of oxidation and reduction, thereby generating more free-radical species. Thus, phenolphthalein may be a significant source of oxidative stress in physiological systems (Sipe *et al.* 1997).

No evidence is available to suggest that mechanisms by which phenolphthalein causes tumors in experimental animals would not also operate in humans. In rodents, phenolphthalein caused oxidative stress and altered tumor-suppressor gene pathways, both of which are mechanisms believed to be involved in human cancer.

Since phenolphthalein was listed in the *Ninth Report on Carcinogens*, an additional study relevant to mechanisms of carcinogenesis has been identified. Dietary administration of phenolphthalein to transgenic mice with the human *c-Ha-ras* proto-oncogene promoted the development of lung cancer (adenocarcinoma) induced by a single intraperitoneal injection of *N*-ethyl-*N*-nitrosourea (*N*-nitroso-*N*-ethylurea, which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*) (Imaoka *et al.* 2002).

Properties

Phenolphthalein is a benzofuran derivative that exists as an odorless white or yellowish white triclinic crystal at room temperature (NTP 1996, Akron 2009). It is practically insoluble in water, but is soluble in dilute solutions of alkali hydroxides, ether, acetone, pyrene, chloroform, toluene, and ethanol. It is insoluble in benzene and petroleum ether (NTP 1996, HSDB 2009). Phenolphthalein is not flammable (Akron 2009). Phenolphthalein-titrated solutions are colorless at pH less than 8.5 and pink to deep red at pH greater than 9 (NTP

1996). Physical and chemical properties of phenolphthalein are listed in the following table.

Property	Information
Molecular weight	318.3 ^a
Specific gravity	1.277 at 32°C ^a
Melting point	262.5°C ^a
Log K_{ow}	2.41 ^a
Water solubility	0.4 g/L at room temperature ^a
Vapor pressure	6.7×10^{-13} mm Hg at 25°C ^b
Vapor density relative to air	11 ^c
Dissociation constant (pK _a)	9.7 at 25°C ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Phenolphthalein in 1% alcoholic solution is used as a visual indicator in titrations of mineral and organic acids and most alkalis (IARC 2000). One of the indicator uses of phenolphthalein is to determine the depth of concrete carbonation (Chang and Chen 2006), which is an indicator of the start of corrosion. Phenolphthalein has also been used in a variety of ingested products and in some scientific applications (NTP 1996). It is odorless and tasteless, and has been incorporated in tablets, powders, and liquids for use as a laxative. Over-the-counter chocolate or gum laxative products containing phenolphthalein formerly were available worldwide. However, in 1999, phenolphthalein was removed from the U.S. Food and Drug Administration's list of products generally recognized as safe and effective for use in over-the-counter stimulant laxatives (FDA 1999). Phenolphthalein has also been used to test for dilute blood in forensic applications. Phenolphthalein was as sensitive as other common indicators of blood, but was not as specific as other reagents for blood in a variety of substrates, and it reduced the amount of DNA in the sample that could be used for further identification (Tobe *et al.* 2007).

Production

In 1997, the year the FDA proposed reclassification of the use of phenolphthalein in over-the-counter laxative products, 20 manufacturers produced phenolphthalein-containing laxatives (FDA 1997). In 2009, phenolphthalein was produced by eight manufacturers worldwide, including one each in the United States and China and six in India (SRI 2009), and was available from 57 suppliers, including 34 U.S. suppliers (ChemSources 2009).

Exposure

The routes of human exposure to phenolphthalein are ingestion, dermal contact, and inhalation of contaminated air originating from process units manufacturing the compound (HSDB 2009). The general population has been exposed to phenolphthalein through its common use as an over-the-counter drug, particularly as a laxative. The typical oral dose of phenolphthalein as an over-the-counter laxative was 30 to 200 mg for adults and children aged 12 years or older; the recommended dose was not to exceed 270 mg. Children's doses were 15 to 30 mg for children aged 2 to 5 years and 30 to 60 mg for children aged 6 to 11 years (IARC 2000). Phenolphthalein also has been found as an undeclared drug in several weight-loss products that are marketed as dietary supplements (FDA 2009).

Many studies have shown that the use of laxatives to relieve constipation and to maintain regularity in bowel habits is widespread in the United States; however, few studies reported on the prevalence of phenolphthalein laxative use. From studies of four U.S. populations, it would appear that no more than 10% of the U.S. population used phenolphthalein-containing laxatives as often as once per month, but up to 5% may have used them weekly or more often (Everhart *et al.*

1989, Harari *et al.* 1996). In one case-control study of invasive adenocarcinoma in the state of Washington, with 424 cases and 414 control subjects aged 30 to 62 years, 13.6% of the subjects (cases plus controls) reported constipation requiring treatment (use of a laxative, enema, or prunes) 12 or more times per year, 4.7% reported ever using phenolphthalein laxatives, and 3.5% reported use of phenolphthalein laxatives at least 350 times in their lifetimes (Jacobs and White 1998). In three case-control studies of adenomatous colorectal polyps in U.S. populations (two groups in North Carolina and one in California, each with a mean age between 59 and 62 years and 268 to 813 subjects, about equally divided between cases and controls), 0.97% to 5.1% of the subjects reported using phenolphthalein laxatives at least once a week. The frequent phenolphthalein laxative users accounted for 8% to 30% of all frequent laxative users; in the two North Carolina groups, the figures were 17.5% and 25%, with 10% and 7% using phenolphthalein laxatives at least once a month (Longnecker *et al.* 1997).

Occupational exposure could occur through inhalation or dermal contact during the manufacture, formulation, packaging, or administration of drugs containing phenolphthalein (HSDB 2009). Other exposures occur from the use of phenolphthalein in the laboratory setting. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 75,243 workers (26% female) potentially were exposed to phenolphthalein (NIOSH 1990); of these, 20,122 (65% female) were employed in the Health Services industry. Occupational exposure also occurs during the use of phenolphthalein in forensic applications and in determining the depth of carbonation of concrete in paved surfaces (Chang and Chen 2006).

Regulations

Food and Drug Administration (FDA)

Over-the-counter drug products containing phenolphthalein for use as a stimulant laxative are no longer generally recognized as safe and effective.

When used in laxatives, a warning must be provided that the product should not be used when abdominal pain, nausea, or vomiting are present and that frequent or prolonged use may result in dependence on laxatives. Additionally, the following cautionary statement must be provided: "If skin rash appears, do not use this or any other preparation containing phenolphthalein."

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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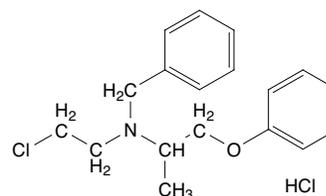
Tobe SS, Watson N, Nic Daéid N. 2007. Evaluation of six presumptive tests for blood, their specificity, sensitivity, and effect on high molecular-weight DNA. *J Forensic Sci* 52(1): 102-109.

Phenoxybenzamine Hydrochloride

CAS No. 63-92-3

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)



Carcinogenicity

Phenoxybenzamine hydrochloride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to phenoxybenzamine hydrochloride by injection caused tumors in two rodent species and at two different tissue sites. Intraperitoneal injection of phenoxybenzamine hydrochloride caused cancer of the abdominal cavity (sarcoma of the peritoneum) in mice and rats of both sexes (NCI 1978, IARC 1980). In strain A mice (a strain with a high spontaneous incidence of lung cancer), intraperitoneal

injection of phenoxybenzamine (the free amine) increased the incidence of lung tumors in both sexes (IARC 1980).

Cancer Studies in Humans

The data available from epidemiological studies for phenoxybenzamine hydrochloride are inadequate to evaluate the relationship between human cancer and exposure specifically to phenoxybenzamine hydrochloride. Since phenoxybenzamine hydrochloride was listed in the *Fifth Annual Report on Carcinogens*, two case reports of patients receiving long-term treatment with phenoxybenzamine have been identified. Chronic lymphocytic leukemia and urinary-bladder cancer (small-cell and squamous-cell carcinoma) were reported in one case (Vaidyanathan *et al.* 2006) and cancer of the esophagus (squamous-cell carcinoma) in the other case (Nettesheim *et al.* 2003).

Properties

Phenoxybenzamine hydrochloride is the hydrochloride salt of a haloalkylamine (closely related chemically to the nitrogen mustards) that exists as a white crystalline powder at room temperature (Akron 2009). It is sparingly soluble in water, soluble in ethanol, chloroform, and propylene glycol, and insoluble in diethyl ether (IARC 1980). It is unstable in neutral and alkaline solutions and is sensitive to oxidation and photodegradation. Physical and chemical properties of phenoxybenzamine hydrochloride are listed in the following table.

Property	Information
Molecular weight	340.3
Melting point	137.5°C to 140°C
Log K_{ow}	3.12
Water solubility	15.2 mg/L at 25°C
Vapor pressure	5.56×10^{-12} mm Hg at 25°C

Source: ChemIDplus 2009.

Use

Phenoxybenzamine hydrochloride is an α -adrenergic receptor blocking agent that was used in the past to treat peripheral vascular disorders such as Raynaud's disease, to control hypertension, and to treat phlebitis, phlebothrombosis, diabetic gangrene, causalgia, chronic skin ulcers, and shock (NCI 1978, IARC 1980). It is now used primarily to treat hypertension and sweating caused by pheochromocytoma (MedlinePlus 2009). It may also be used to treat urinary-bladder problems such as urgency and frequency of urination and inability to control urination in patients with neurogenic bladder, functional outlet obstruction, or partial prostatic obstruction.

Production

Phenoxybenzamine hydrochloride has been produced commercially in the United States by one company since 1953 (IARC 1980). In 2009, it was available from 11 U.S. suppliers (ChemSources 2009). No data on amounts of U.S. production, imports, or exports of phenoxybenzamine hydrochloride were found.

Exposure

The only potential route of human exposure to phenoxybenzamine hydrochloride is ingestion during its medical use. The usual adult dosage is 10 mg twice a day, increasing to 20 to 40 mg two or three times a day, as long as there are no adverse effects on blood pressure (Mayo Clinic 2009). For children, the dose is based on body weight and typically begins at 0.2 mg/kg of body weight once a day, but may increase to 0.4 to 1.2 mg/kg given daily in three or four divided doses. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 797 workers, including 406 women, potentially were exposed to phenoxybenzamine hydrochloride (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Phenoxybenzamine hydrochloride is regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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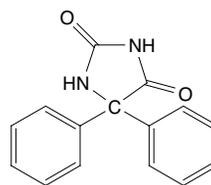
Phenytoin and Phenytoin Sodium

CAS Nos. 57-41-0 and 630-93-3

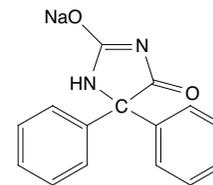
Reasonably anticipated to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Also known as diphenylhydantoin, 5,5-diphenylhydantoin, or Dilantin (a registered trademark of Warner-Lambert Co., LLC)



Phenytoin



Phenytoin sodium

Carcinogenicity

Phenytoin and its sodium salt are *reasonably anticipated to be human carcinogens* based on sufficient evidence from studies in experimental animals.

Cancer Studies in Experimental Animals

Phenytoin as its sodium salt caused lymphoma and leukemia in mice by two different routes of exposure. Administration of phenytoin sodium in a liquid diet caused thymic and generalized lymphoma in females, and administration by intraperitoneal injection caused leukemia and thymic and mesenteric lymphoma in both sexes (IARC 1977).

Since phenytoin and phenytoin sodium were listed in the *First Annual Report on Carcinogens*, additional studies in rodents have been identified. The effects of phenytoin in mice and rats were evaluated following dietary exposure of adults, perinatal exposure (*in utero* and via lactation), or combined perinatal and adult exposure. In mice, phenytoin caused liver tumors in females after adult-only exposure or combined perinatal and adult exposure and in males after combined perinatal and adult exposure; liver-tumor incidence was not significantly increased in male mice after adult-only exposure. In rats, phenytoin marginally increased the incidence of liver tumors in males after adult-only exposure or combined perinatal and adult exposure; however, the effect was not enhanced by the combined exposure (NTP 1993).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to phenytoin. Several case reports and case series linked cancer outcomes to treatment with phenytoin, including reports of lymphoma among individuals undergoing phenytoin therapy, but no significant excess of lymphoma was reported in two small follow-up studies of lymphoma among epilepsy patients (IARC 1977).

Since phenytoin and phenytoin sodium were listed in the *First Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer concluded that there was inadequate evidence for the carcinogenicity of phenytoin in humans (IARC 1996). In studies of brain and central nervous system cancer in patients given phenytoin for epilepsy, significantly increased risks were observed in a cohort mortality study of patients treated with phenobarbital and phenytoin (White *et al.* 1979) and in two cohort incidence studies of patients treated with phenytoin (with or without phenobarbital) (Olsen *et al.* 1989, Selby *et al.* 1989). However, IARC noted that brain tumors could have been the cause of the seizure disorder and were unlikely to be drug related. Findings from case-control studies were inclusive (IARC 1996).

Properties

Phenytoin is a white, odorless powder at room temperature (Akron 2009). It is practically insoluble in water, but it is soluble in acetone, ethanol, and alkali hydroxides (IARC 1996). It is stable under normal temperatures and pressures (Akron 2009). The only physical property identified for phenytoin sodium (molecular weight = 274.2) was its solubility in water (1 g in ~66 mL) and its insolubility in ether and chloroform (HSDB 2009). Phenytoin sodium dissociates easily to regenerate phenytoin, even in weakly acidic solutions. Phenytoin may also be administered as the water-soluble prodrug fosphenytoin (molecular weight = 362.3) or its disodium salt (molecular weight = 406.2), which are converted to phenytoin by phosphatases in the liver (McNamara *et al.* 2001). Fosphenytoin solubility in water is estimated as 349 mg/L at 25°C, and fosphenytoin disodium salt is soluble at 142 mg/mL at 25°C (O'Neil *et al.* 2006). Physical and chemical properties of phenytoin are listed in the following table.

Property	Information
Molecular weight	252.3 ^a
Density	1.29 g/cm ^{3b}
Melting point	286°C ^b
Log K_{ow}	2.47 ^b
Water solubility	0.032 g/L at 22°C ^b
Vapor pressure	1.2×10^{-10} mm Hg at 25°C ^b
Dissociation constant (pK _a)	8.33 ^c

Sources: ^aAkron 2009, ^bChemIDplus 2009, ^cHSDB 2009.

Use

Phenytoin is an anticonvulsant drug used alone or in combination with phenobarbital or other anticonvulsant drugs to treat patients with tonic-clonic (grand mal), focal, and psychomotor seizures (IARC 1977, 1996). It can be used to control seizures occurring during neurosurgery and to reverse digitalis-induced arrhythmia. Phenytoin is also used in a 10% ointment formulation to promote healing of ulcers in patients with diabetes (Younes *et al.* 2006). Phenytoin has been used in the treatment of chorea or Parkinson's syndrome to control involuntary movements (IARC 1977, HSDB 2009). In the past, phenytoin was used to treat acute alcoholism, migraine, polyneuritis, pregnancy disorders, certain psychoses, and trigeminal neuralgia. Phenytoin is also used to control seizures in dogs (IARC 1977, 1996, NTP 1993).

Production

Commercial production of phenytoin was first reported in the United States in 1946 (IARC 1977). U.S. sales totaled 1,093,250 standard dosage units in 1990 and 984,527 in 1995 (IARC 1996). In 2009, phenytoin was produced by four manufacturers in Europe, three in South or Central America, and one in India and (SRI 2009); it was available from 14 U.S. suppliers (ChemSources 2009), and 35 pharmaceutical products contained phenytoin as an active ingredient (FDA 2009a).

Exposure

The routes of potential human exposure to phenytoin are injection, ingestion, inhalation, and dermal contact (NTP 1993, HSDB 2009). Statistics on the number of patients using phenytoin were not available, but the drug is widely used by individuals suffering from epilepsy (Epilepsy.com 2007). Phenytoin is the active ingredient in seven oral pharmaceutical products, and sodium phenytoin in nine oral products and four injectable formulations (Drugs.com 2009b). Fosphenytoin, which is a phosphate ester prodrug converted to phenytoin (Browne *et al.* 1996), is available in one short-term injectable formulation used to administer phenytoin to individuals who cannot take an oral medication (e.g., during status epilepticus) (Drugs.com 2009a). The initial oral dosage of phenytoin for adults and children over 6 years of age is 100 mg 3 times per day; the dosage may be gradually increased by 100 mg every two to four weeks until the desired therapeutic response is obtained. Daily maintenance dosages usually range from 300 to 600 mg for adults and 3 to 10 mg/kg of body weight for children under 6 years of age (NTP 1993). As a cardiac depressant, phenytoin is usually administered in an oral dose of 100 mg two to four times per day or by intravenous injection of 50 to 100 mg every 10 to 15 minutes up to a maximum dose of 10 to 15 mg/kg of body weight (IARC 1977). Patients with large diabetic ulcers may receive dermal applications of an ointment containing 10% phenytoin to promote healing (Younes 2006). Phenytoin is also given for pain associated with peripheral neuropathy, for bipolar disorder, and for localized scleroderma; usual therapeutic levels are 10 to 20 µg/mL in blood (SF 2008, MedlinePlus 2009). In 2009, 48 clinical trials involving phenytoin were in progress or recently completed, including 22 that were recruiting patients in the United States (ClinicalTrials

2009). Phenytoin was also found as an undeclared drug in several weight-loss products marketed as dietary supplements (FDA 2009b).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of phenytoin before 2007 ranged from 8,000 to 20,000 lb except in 2002, when no releases were reported, and in 2003, when 41,000 lb was released. In 2007, one facility released 40 lb of phenytoin to air (TRI 2009).

Occupational exposure to phenytoin may occur among workers involved in formulation and packaging of the pharmaceutical products and health professionals involved in its preparation and administration. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 23,400 workers, including 16,795 women, potentially were exposed to phenytoin (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act Toxics Release Inventory: Listed substance subject to reporting requirements.

Food and Drug Administration (FDA)

Phenytoin is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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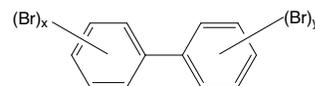
Polybrominated Biphenyls

Separate CAS Nos. are assigned to individual polybrominated biphenyls

Reasonably anticipated to be human carcinogens

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as PBBs



Polybrominated biphenyls (number of bromine atoms $[x + y] = 1-10$)

Carcinogenicity

Polybrominated biphenyls (PBBs) are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The animal studies used FireMaster FF-1, which is a commercial mixture of polybrominated biphenyl isomers, containing a mixture of pentabromobiphenyls, hexabromobiphenyls, and heptabromobiphenyls.

Cancer Studies in Experimental Animals

Oral exposure to PBBs caused liver tumors in mice and rats. Administration of a commercial mixture of polybrominated biphenyl isomers (FireMaster FF-1) by stomach tube caused liver cancer (hepatocellular carcinoma) in mice and rats of both sexes and bile-duct cancer (cholangiocarcinoma) in rats of both sexes (NTP 1983).

Since PBBs were listed in the *Third Annual Report on Carcinogens*, additional studies in rats and mice have been identified. These studies evaluated the effects of PBBs (FireMaster FF-1) in mice and rats, after (1) dietary exposure of adults, (2) perinatal exposure (dietary exposure of dams prior to breeding and throughout gestation and lactation), and (3) the combined effects of perinatal and adult exposure (NTP 1993). Increased incidences of liver cancer (hepatocellular carcinoma) were observed after dietary exposure of adult mice and rats of both sexes and perinatal exposure of mice of both sexes. In female rats, combined perinatal and adult exposure increased the incidence of liver cancer, compared with adult exposure only. In mice, the high incidence of liver cancer in mice exposed only as adults limited the study's ability to evaluate the combined effects of perinatal and adult exposure on tumor incidence; however, combined exposure

increased the number of tumors per animal, compared with adult exposure only, suggesting an enhancing effect.

Cancer Studies in Humans

No epidemiological studies that evaluated the relationship between human cancer and exposure specifically to PBBs were identified at the time they were listed in the *Third Annual Report on Carcinogens*. Since then, a few epidemiological studies have been identified. The International Agency for Research on Cancer reviewed the evidence available in 1986 and concluded that there were no informative studies. Since the IARC evaluation, a case-control study of participants in a PBB-exposure registry in Michigan has been published, which found significant exposure-level-related increases (based on serum PBB concentration) in lymphoma and digestive-system cancer (Hoque *et al.* 1998). Other studies were uninformative.

Properties

PBBs are a class of biphenyl compounds with one to ten hydrogen atoms replaced by bromine. PBBs with three or more bromine atoms are solids with low volatility; volatility decreases with increasing numbers of bromine atoms. PBBs are usually white, off-white, or beige powders at room temperature (IPCS 1994). All of the congeners are insoluble in water but readily soluble in fat. PBBs are extremely stable and therefore persistent in the environment. Hexabromobiphenyl (C₁₂H₄Br₆, CAS No. 36355-01-8), one of 101 PBBs compounds in the CAS Registry system, is the main component of the commercial PBB mixtures tested in animal carcinogenicity studies as FireMaster FF-1 (FireMaster was registered as a trademark by the Michigan Chemical Corporation, St. Louis, MI). FireMaster FF-1 was produced by grinding FireMaster BP-6, the other main commercial hexabromobiphenyl PBB mixture (of which the major components were 4.0% pentabromobiphenyls, 62.6% hexabromobiphenyls, and 33.4% heptabromobiphenyls) and blending it with 2% calcium polysilicate as an anticaking agent (NTP 1993). Physical and chemical properties of hexabromobiphenyl, as a representative PBB, are listed in the following table.

Property	Information
Molecular weight	627.6
Melting point	72°C
Log K _{ow}	6.39
Water solubility	0.011 mg/L at 25°C
Vapor pressure	5.2 × 10 ⁻⁸ mm Hg at 25°C

Source: ChemIDplus 2010.

Use

PBBs are no longer used in the United States. Previously, they were used as flame-retardant additives in synthetic fibers and molded plastics. Their major applications were in thermoplastics, mainly acrylonitrile-butadiene-styrene used in electronic-equipment housings. Hexabromobiphenyl was the primary component of the two major products previously used as fire retardants in business-machine housings and in industrial and electrical products. PBBs were also used in smaller amounts as a fire retardant in lacquers and coatings, and in automobile upholstery (ATSDR 2004).

Production

PBBs are no longer produced in commercial quantities in the United States. Three PBB isomers formerly were produced commercially, including hexabromobiphenyl, octabromobiphenyl (CAS No. 61288-13-9), and decabromobiphenyl (CAS No. 13654-09-6). All technical-grade PBBs contained mixtures of several brominated isomers. The sole U.S. producer of hexabromobiphenyl ceased produc-

tion in November 1974 because of a 1973 incident in Michigan in which the chemical was mistaken for a nutrient additive and 2,000 lb of it was added to animal feed, resulting in the destruction of thousands of farm animals and exposure of many Michigan residents. In 1970, 9,500 kg (21,000 lb) of hexabromobiphenyl and 14,100 kg (31,000 lb) of octabromobiphenyl and decabromobiphenyl were produced. From 1970 to 1974, 11 million pounds of hexabromobiphenyl was produced under the trade names FireMaster BP-6 and FireMaster FF-1. One U.S. firm produced octabromobiphenyl and decabromobiphenyl from 1970 to 1979, and another U.S. firm produced decabromobiphenyl from 1973 to sometime prior to 1977. Estimated U.S. production of PBBs was 170,000 lb in 1975; in 1976, it was 807,000 lb, of all of which was exported (IARC 1986). In 2009, decabromobiphenyl was produced by one company each in China and Europe (SRI 2009) and was available from five suppliers, including three U.S. suppliers (ChemSources 2009). No suppliers were identified worldwide for either hexabromobiphenyl or octabromobiphenyl.

Exposure

The routes of potential human exposure to PBBs are ingestion, inhalation, and dermal contact. Residues remaining in and around facilities that formerly manufactured, processed, or produced products using PBBs are current sources of exposure. In 1973 and 1974, 8,000 to 12,500 Michigan residents were exposed to meat, milk, butter, cheese, and eggs contaminated with PBBs. A general-population survey subsequently conducted in Michigan found that 90% of the population had detectable levels of PBBs in their blood (IARC 1978). In 1976, 524 dairy farmers had a median PBB serum concentration of 2.6 µg/L. In a study conducted in Michigan from 1976 to 1977, 3,639 individuals (mainly farm residents and chemical workers) had a median serum PBB concentration of 3.0 µg/L. Another 1977 study of 3,683 Michigan residents found serum PBB concentrations ranging from less than 1 to 3,150 µg/L, with a geometric mean of 4.1 µg/L. Because PBBs are biologically stable and eliminated slowly, significant body burdens could persist throughout the lifetimes of exposed individuals (IARC 1986).

PBBs have been replaced by polybrominated diphenyl ethers (PBDEs) as brominated fire retardants in textiles, electronic equipment, and plastics (Hanari *et al.* 2006). However, PBBs have been detected as impurities in PBDEs, at concentrations of total PBBs ranging from 58 to 4,025 ng/g in PBDE products. It was estimated that approximately 40 kg of PBBs were emitted annually as a result of the production and use of PBDEs.

In a 1993 study of sport fishers on the Great Lakes (Huron, Michigan, and Erie), those who consumed fish from Lake Huron had the highest mean PBB serum concentration, at 0.6 ng/mL (0.6 µg/L). When the data were stratified by state, sport fishers from Michigan had the highest mean serum concentration, at 0.7 ng/mL (0.7 µg/L) (Anderson *et al.* 1998). In a 1997 study, PBBs were measured in lake trout in the Great Lakes; the mean concentration was highest in fish from Lake Huron, at 3.1 ng/g of wet weight, and lowest in fish from Lake Superior, at 0.13 ng/g (Luross *et al.* 2002). Thirty years after production of PBBs ceased, these compounds were still detectable in the floodplain soils and sediments of Michigan's Pine River, Tittabawassee River, Saginaw River, and Saginaw Bay (Yun *et al.* 2008). A mean concentration of 13.5 ng/g of dry weight in floodplain soil was reported in the lower reaches of the Pine River, near the source of contamination, and a mean concentration of 4.7 ng/g was reported for sediment from the mouth of the Saginaw River, an estimated distance of over 90 km from the source.

In the 2003–04 National Health and Nutrition Examination Survey, BB-153 (hexabromobiphenyl) was evaluated in the serum lipid

of 2,032 adults nationwide and was detected in 83%, at a geometric mean concentration of 2.3 ng/g of lipid. Concentrations were highest in U.S.-born individuals over the age of 60 living in houses constructed before 1977 (Sjödín *et al.* 2008). These results corroborated previous findings that showed declining levels of BB-153 in serum from analysis of archived U.S. serum samples collected from 1985 to 2002 (Sjödín *et al.* 2004). The median BB-153 serum concentration was 8.0 ng/g of lipid for 1985 to 1989 and fell in each subsequent reporting period, reaching 3.3 ng/g for 2000 to 2002. BB-153 serum concentration was inversely correlated with collection year ($R = -0.51$, $P < 0.01$).

Workers at companies that manufactured PBBs may have been exposed by skin contact, inhalation, or unintentional ingestion. At one U.S. manufacturer, hexabromobiphenyl was detected at concentrations of 1.1 to 1,729 ppb in the workers' serum and 0.51 to 581 ppm in their adipose tissue (IPCS 1994). At an electronics recycling facility in Sweden, PBBs were measured in air at concentrations of up to 57 ng/m³ near a shredder that ground plastic housings of electronic equipment containing brominated fire retardants and 0.024 ng/m³ in the area where new circuit boards were assembled from recycled materials (Sjödín *et al.* 2001).

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed category of substances subject to reporting requirements.

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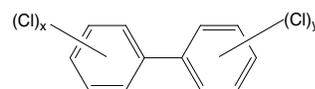
Polychlorinated Biphenyls

CAS No. 1336-36-3

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as PCBs or chlorodiphenyls



Polychlorinated biphenyls (number of chlorine atoms $[x + y] = 1-10$)

Carcinogenicity

Polychlorinated biphenyls (PCBs) are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. Not all PCB mixtures caused tumors in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to PCBs caused liver tumors in mice and rats. In male mice, dietary administration of mixtures of PCBs with similar average chlorine content — Aroclor 1254 (approximately 54% chlorine by weight) and Kanechlor 500 (52% to 54% chlorine by weight) — caused benign and/or malignant liver tumors (hepatocellular adenoma or carcinoma). In female rats, dietary administration of Aroclor 1260 (approximately 60% chlorine by weight) caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) (IARC 1978).

Since PCBs were listed in the *Second Annual Report on Carcinogens*, additional studies of dietary exposure in rats have been identified, which found that (1) additional PCB mixtures or individual congeners caused tumors, (2) specific PCB mixtures or congeners caused liver tumors in male rats, and (3) PCB mixtures or congeners caused tumors at additional tissue sites. Dietary exposure to Aroclor 1016, 1242, 1254, or 1260 caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in female rats; liver tumors were observed in male rats after exposure to Aroclor 1260 but not the other mixtures. An additional type of liver tumor (hepatocholangioma) was observed in female rats exposed to Aroclor 1254 (Norback and Weltman 1985, Mayes *et al.* 1998). Another PCB mixture, Clophen A, caused liver cancer (hepatocellular carcinoma) in weanling male rats (Schaeffer *et al.* 1984). PCB mixtures also caused tumors at tissue sites other than the liver: Aroclor 1254 caused gastrointestinal-tract cancer (adenocarcinoma) in rats of both sexes (Morgan *et al.* 1981, Ward *et al.* 1985), Aroclor 1260 caused tumors of the thymus and spleen in male rats (Rao and Banerji 1990), and Aroclor 1242, 1254, or 1260 caused benign thyroid-gland tumors (follicular-cell adenoma) in male rats (Mayes *et al.* 1998).

The National Toxicology Program (NTP 2006a,b,c,d) conducted several studies of exposure to individual PCBs or mixtures of two PCBs by stomach tube in female rats. Incidences of benign and malignant tumors of the bile duct and liver (cholangioma, hepatocholangioma, cholangiocarcinoma, and hepatocellular adenoma) and lung

(squamous-cell carcinoma or cystic keratinizing epithelioma) were increased by exposure to PCB 126 or 118 alone or to mixtures of PCB 126/153 or PCB 126/118. Exposure to the PCB 126/118 mixture also caused cancer of the oral mucosa (gingival squamous-cell carcinoma), and exposure to the PCB 126/153 mixture and to PCB 118 alone also caused uterine cancer (squamous-cell carcinoma) and tumors of the pancreas (acinar tumors).

The International Agency for Research on Cancer concluded that PCB 126 (3,3',4,4',5-pentachlorobiphenyl) was a complete carcinogen in experimental animals. Based on extensive evidence that it acted through the same aryl-hydrocarbon-receptor-mediated mechanism as 2,3,7,8-tetra-chlorodibenzo-*p*-dioxin (TCDD, or dioxin), IARC classified it as carcinogenic in humans (Baan *et al.* 2009).

Cancer Studies in Humans

At the time PCBs were listed in the *Second Annual Report on Carcinogens*, very few epidemiological studies had evaluated the relationship between human cancer and exposure specifically to PCBs. An excess incidence of melanoma was reported in a small group of workers exposed to the PCB mixture Aroclor 1254, but the workers were probably also exposed to other agents (IARC 1978). Since PCBs were listed in the *Second Annual Report on Carcinogens*, numerous epidemiological studies of PCBs and cancer have been identified. In 1987, IARC classified the evidence of carcinogenicity in humans as limited, based primarily on studies reporting excesses of liver and/or bile-duct cancer. Excess liver and bile-duct cancer was reported among women occupationally exposed to PCBs in capacitor manufacturing and individuals exposed to PCBs from contaminated cooking oil. A cohort study of Italian capacitor-manufacturing workers found an excess of gastrointestinal-tract tumors (including liver and bile-duct tumors) among men and lymphohematopoietic cancer among women. However, IARC noted that these studies had a number of limitations, including small numbers of cases, inability to evaluate exposure-response relationships, and possible confounding from exposure to other chemicals (IARC 1987).

Since the 1987 IARC review, additional occupational cohort studies or follow-up studies have been conducted, as well as numerous population-based case-control studies of PCB residues in fat or blood, with exposure primarily from dietary sources. As in the studies reviewed by IARC, increased risks of liver or bile-duct cancer were reported in several cohort and follow-up studies of capacitor workers (Gustavsson and Hogstedt 1997, Mallin *et al.* 2004, Prince *et al.* 2006b); risks increased with increasing cumulative exposure (Prince *et al.* 2006a). One case-control study also reported increased risk of bile-duct cancer (Ahrens *et al.* 2007). However, not all studies found increased risks. Some of the occupational studies and case-control studies found excesses of cancer at other tissue sites, such as the gastrointestinal tract, brain, testes, or skin (malignant melanoma), but the findings were not always consistent across studies. The occupational cohort studies were limited by small numbers and limited exposure assessment; most of the studies did not report PCB levels (Carpenter 2006, Knerr and Schrenk 2006, Golden and Kimbrough 2009). In addition, workers were exposed to mixtures of congeners, and the proportion of each congener could have varied from batch to batch and from study to study (Hopf *et al.* 2009).

Measurement of specific PCBs (or groups of congeners) in the peripheral blood, adipose tissue, or carpet dust was associated with increased risk of non-Hodgkin's lymphoma in most of the population-based nested case-control studies (Hardell *et al.* 1996, Rothman *et al.* 1997, Colt *et al.* 2005, De Roos *et al.* 2005, Engel *et al.* 2007a,b, Spinelli *et al.* 2007), and some of the studies reported exposure-response relationships. Two studies found no evidence of an association be-

tween non-Hodgkin's lymphoma and exposure to PCBs (Fritsche *et al.* 2005, Cocco *et al.* 2008). A retrospective cohort mortality study that followed 1,940 individuals who had been poisoned by ingesting PCB-contaminated oil in Taiwan reported increased mortality from Hodgkin's lymphoma (Hsieh *et al.* 1996). The findings for non-Hodgkin's lymphoma or lymphohematopoietic cancer in occupational retrospective cohort studies were inconsistent (Engel *et al.* 2007b).

Many population-based case-control studies and cohort studies of breast cancer in relation to PCBs in serum, plasma, or adipose tissue have been conducted. In general, cohort studies usually used samples stored prior to cancer diagnosis for measurement of PCB levels. Some studies found positive associations between breast cancer and specific PCB congeners or groups of congeners; however, findings from studies of breast cancer were conflicting (Salehi *et al.* 2008).

Properties

PCBs are a class of biphenyl compounds with one to ten hydrogen atoms replaced by chlorine. At room temperature, they range in physical state from light- to dark-yellow oily liquids to white crystalline solids and hard noncrystalline resins (IPCS 1992, HSDB 2009). PCBs are produced commercially by chlorination of biphenyl, resulting in 209 possible PCB congeners (Silberhorn *et al.* 1990). However, McFarland and Clarke (1989) reported that about half of these molecules accounted for nearly all environmental contamination by PCBs, and they considered only 36 to be environmentally relevant, because of their potential toxicity, environmental prevalence, and relative abundance in animal tissues. Commercial PCB formulations are complex mixtures of chlorinated biphenyls that vary in the degree of chlorination, and similar mixtures can show significant lot-to-lot variation in composition (ATSDR 2000). Of the 209 possible PCB congeners, about 100 are present in commercial PCB mixtures, and about 70 have been detected in human adipose tissue (Mühlebach *et al.* 1991). At least 20 of the 209 possible congeners have not been identified in commercial mixtures of PCBs (Kimbrough 1987).

Physical and chemical properties of PCBs are affected by the numbers and positions of chlorine atoms (Carpenter 2006). PCBs with fewer chlorine atoms tend to be more soluble in water, more volatile, and more easily metabolized. Larger numbers of chlorine atoms are associated with increased resistance to biodegradation, which can increase bioaccumulation in the environment. PCBs are practically insoluble in water, but soluble in organic solvents and fats (IPCS 1992). They are very stable and persistent in the environment. Physical and chemical properties representative of PCBs are listed in the following table.

Property	Information
Molecular weight	292.0 to 360.9 ^a
Specific gravity	1.44 at 30°C ^a
Melting point	340°C to 375°C ^a
Log <i>K</i> _{ow}	7.1 ^b
Water solubility	0.0007 g/L at 25°C ^b
Vapor pressure	0.000494 mm Hg at 25°C ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cSR 2009.

PCBs have been categorized as "dioxinlike" or "non-dioxinlike," based on their ability to exert biochemical and toxic effects similar to those of TCDD through activation of the aryl hydrocarbon receptor (Carpenter 2006, Knerr and Schrenk 2006). Dioxin-like activity is seen for PCB congeners with chlorine atoms occupying meta (carbon atoms 3, 3', 5, or 5') and para (carbon atoms 4 or 4') positions, with no more than one ortho (carbon atoms 2, 2', 6, or 6') chlorine; these molecules are likely to exist with a planar conformation. Twelve tetra-, penta-, hexa-, or hepta-chlorobiphenyls meet these criteria and have been

assigned toxic equivalency factors (TEQs) of 0.0001 to 0.1 by the World Health Organization based on their toxicity relative to that of TCDD, which has the highest toxic potency for activation of the aryl hydrocarbon receptor (TEQ = 1.0). PCB 126 has a TEQ of 0.1, which is the highest value for this class of molecules.

Use

Before 1974, PCBs were used in the United States for both enclosed applications, such as transformers, capacitors, and heat transfer and hydraulic fluids, and open applications, such as inks, flame retardants, adhesives, carbonless duplicating paper, paints, plasticizers, wire insulators, metal coatings, and pesticide extenders (IARC 1978, ATSDR 2000). After 1974, all uses of PCBs were limited to enclosed applications (transformers and capacitors), and after January 1979, no PCBs were used in the manufacturing of transformers or capacitors. The only remaining permitted uses of PCBs are as a mounting medium in microscopy, as an immersion oil in low-fluorescence microscopy, as an optical liquid, and for other research and development purposes (ATSDR 2000).

Production

PCBs were first produced commercially in the United States in 1929. They are no longer produced in the United States except for limited uses in research and development (IARC 1978). Four Aroclor mixtures — 1016, 1242, 1254, and 1260 — accounted for 92% of all PCB production between 1958 and 1977 (Mayes *et al.* 1998). The chlorination reaction was stopped when the chlorine content reached 42% for Aroclor 1242, 54% for 1254, and 60% for 1260. Aroclor 1016 was produced with a chlorine content of 41% by fractional distillation of Arochlor 1242, a process that excluded more highly chlorinated congeners, which have higher boiling points. Since 1970, nine PCB mixtures (Aroclor 1016, 1221, 1232, 1242, 1248, 1254, 1260, 1262, and 1268) accounted for 35% of all PCBs commercially produced and 98% of the PCBs sold in the United States. Domestic production peaked at 85 million pounds in 1970, decreasing to about 41 million pounds by 1974, when the Monsanto Chemical Company produced an estimated 40 million pounds of PCBs. Kanechlors were PCB mixtures produced in Japan, and Clophens were PCB mixtures produced in Germany. U.S. import or export of PCBs has not been permitted since 1979 (ATSDR 2000).

Exposure

The primary routes of potential human exposure to PCBs are ingestion, inhalation, and dermal contact (ATSDR 2000). The release of PCBs from prior industrial uses and their persistence in the environment have resulted in widespread contamination of water and soil. PCBs were identified at 500 of 1,598 hazardous-waste sites proposed for inclusion on the U.S. Environmental Protection Agency's National Priorities List. For 2007, EPA's Toxics Release Inventory listed 57 facilities that produced, processed, or otherwise used PCBs and released a total of 2,307,203 lb of PCB wastes to land (TRI 2009).

New stocks of PCBs are no longer produced; however, existing quantities of PCBs are continually redistributed through the global environment by human activity and natural processes (ATSDR 2000). PCBs have been measured in air, water, soil, and human tissues in all parts of the world. PCBs are released to air from contaminated soil, water, and hazardous-waste sites, and atmospheric transport is the most common mechanism for global dispersion. Although the concentration of vapor-phase PCBs can be significantly elevated near PCB-contaminated hazardous waste sites, the more volatile congeners can dissipate relatively rapidly. PCBs in the atmosphere may be deposited to soil, water, and plants at distant sites by settling and by

washout from precipitation. Once in water, PCBs may be removed by revolatilization to the atmosphere, uptake by fish or other organisms, or sedimentation and burial. Most of the PCBs lost from the waters of the Great Lakes were revolatilized to the atmosphere. PCBs may also enter organisms directly from the water and biomagnify through the aquatic food web. Edible fish from contaminated water bodies, particularly fresh water, are a major source of human exposure to PCBs.

The relative concentrations of PCB congeners change as a result of physical and chemical processes and selective bioaccumulation and biotransformation as they move through the environment, including living organisms (Beyer and Biziuk 2009). The mixtures resulting from these processes differ substantially from the original material. PCBs in the biosphere are mainly penta-, hexa-, and heptachlorinated congeners, with an average chlorine content of over 50%. In contrast, the average chlorine content of commercially used mixtures was less than 42% (Mühlebach *et al.* 1991). Dehalogenation can occur in fresh-water and estuarine sediments. PCBs can also be biodegraded aerobically or anaerobically by bacteria or other microorganisms (Beyer and Biziuk 2009). Metabolism of PCBs requires at least one pair of adjacent unchlorinated carbon atoms that can result in initial formation of an arene oxide (Mühlebach *et al.* 1991).

A major source of human exposure to PCBs is dietary (IARC 1978). Because PCBs are soluble in fats and oils, the major U.S. commodities in which PCBs have been found are fish, cheese, eggs, and animal feed. PCB residues have been detected in human milk and fat samples collected from the general U.S. population. The average daily human intake of PCBs via food was estimated at 0.027 $\mu\text{g}/\text{kg}$ in 1978, but declined to less than 0.001 $\mu\text{g}/\text{kg}$ in 1991 (ATSDR 2000). PCBs have frequently been identified at relatively high concentrations in the blood, fat, and milk of native Inuit populations living in Arctic regions, whose diet is high in fish and marine animals. For example, the mean concentration of PCBs in fat tissue collected from a native population in Greenland was 5,719 $\mu\text{g}/\text{kg}$ of lipid, and the concentrations were highest in older individuals. PCBs also accumulate in the breast milk of women in this population. In a 1989–90 study, the mean PCB concentration in breast milk from native Inuit women who consumed large quantities of marine mammal tissue was 1,052 ng/g ($\mu\text{g}/\text{kg}$) of lipid, resulting in a high daily intake by their infants (10 $\mu\text{g}/\text{kg}$). Based on data from the Second National Health and Nutrition Examination Survey (conducted from 1976 to 1980), the median serum PCB concentration in the United States was estimated at 4.2 $\mu\text{g}/\text{L}$. The concentrations were higher in individuals who regularly ate fish than in those who occasionally or never ate fish (Humphrey *et al.* 2000). In 2000, it was reported that serum PCB concentrations in individuals without unusual exposure had ranged from about 0.9 to 1.5 ppb in recent years (ATSDR 2000). PCB concentrations in humans increase with age. The half-life of PCBs in human blood serum is 3 to 5 years for high serum concentrations and 13 to 17 years for lower serum concentrations (Carpenter 2006).

EPA estimated that people within 12 miles of commercial incinerators might be exposed to PCBs released to air (ATSDR 2000). Incineration has declined as a method for disposal of PCB-contaminated materials, because incineration can be incomplete if the combustion temperature is not high enough, leading to formation of highly toxic by-products, such as hydrogen chloride, polychlorinated dibenzodioxins, and polychlorinated dibenzofurans (Beyer and Biziuk 2009).

In 1977, the National Institute for Occupational Safety and Health estimated that 12,000 workers potentially were exposed to PCBs (ATSDR 2000).

Regulations

Coast Guard, Department of Homeland Security

Shipboard incineration of PCBs is prohibited.

Department of Transportation (DOT)

PCBs are considered hazardous substances and marine pollutants, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.000064 µg/L; based on fish or shellfish consumption only = 0.000064 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed category of substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.0005 mg/L.

Toxic Substances Control Act

Extensive regulations governing the manufacturing, processing, distribution in commerce, use, and disposal of PCBs have been developed.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0005 mg/L (as decachlorobiphenyl).

The action level for PCBs in red meat is 3 ppm (fat basis).

Specific provisions are set to prevent PCBs contamination in establishments manufacturing food-packaging materials.

Specific provisions are set to prevent PCBs contamination in the production, handling, and storage of animal feed.

Temporary tolerances for PCBs in milk, dairy products, poultry, eggs, fish and shellfish, and infant food range from 0.2 to 2 ppm.

Temporary tolerances for PCBs in animal feed range from 0.2 to 10 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.5 mg/m³ for chlorodiphenyl 54% chlorine; = 1.0 mg/m³ for chlorodiphenyl 42% chlorine.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 5 mg/m³.

Recommended exposure limit (REL) = 0.001 mg/m³.

Listed as a potential occupational carcinogen.

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Polycyclic Aromatic Hydrocarbons: 15 Listings

Reasonably anticipated to be human carcinogens

Also known as PAHs or polynuclear aromatic hydrocarbons

The term “polycyclic aromatic hydrocarbon” (PAH) commonly refers to a large class of organic compounds that contain carbon and hydrogen and consist of two or more fused aromatic rings. Fifteen individual PAHs (not the entire class) are listed separately in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*:

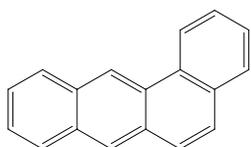
- Benz[*a*]anthracene, benzo[*b*]fluoranthene, benzo[*j*]fluoranthene, benzo[*a*]pyrene, dibenz[*a,h*]acridine, dibenz[*a,j*]acridine, dibenz[*a,h*]anthracene, 7*H*-dibenzo[*c,g*]carbazole, dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, and indeno[1,2,3-*cd*]pyrene were first listed in the *Second Annual Report on Carcinogens* (1981).
- Benzo[*k*]fluoranthene, dibenzo[*a,e*]pyrene, dibenzo[*a,l*]pyrene, and 5-methylchrysene were first listed in the *Fifth Annual Report on Carcinogens* (1989).

The chemical structures of the 15 listed PAHs are shown below. Evidence for their carcinogenicity from studies in experimental animals is then discussed separately for each PAH. However, most of the information on mechanisms of carcinogenesis, cancer studies in humans, use, production, exposure, and regulations is common to all 15 listed PAHs and therefore is discussed for the overall class of PAHs, following the discussions of cancer studies in experimental animals.

Benz[*a*]anthracene

CAS No. 56-55-3

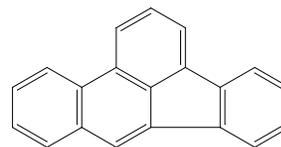
Also known as BA



Benzo[*b*]fluoranthene

CAS No. 205-99-2

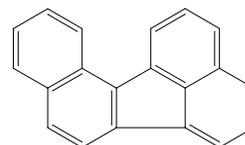
Also known as B[*b*]F



Benzo[*j*]fluoranthene

CAS No. 205-82-3

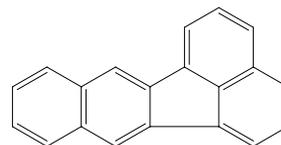
Also known as B[*j*]F



Benzo[*k*]fluoranthene

CAS No. 207-08-9

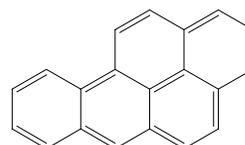
Also known as B[*k*]F



Benzo[*a*]pyrene

CAS No. 50-32-8

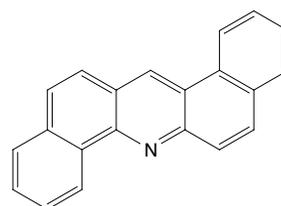
Also known as B[*a*]P



Dibenz[*a,h*]acridine

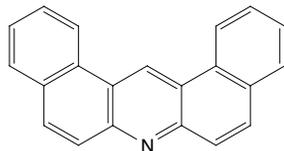
CAS No. 226-36-8

Also known as DB[*a,h*]AC

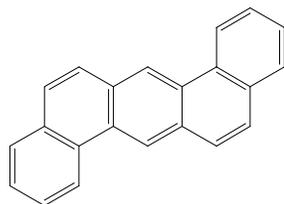


Dibenz[*a,j*]acridine

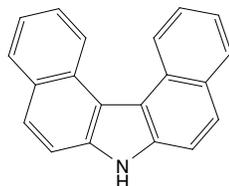
CAS No. 224-42-0

Also known as DB[*a,j*]AC**Dibenz[*a,h*]anthracene**

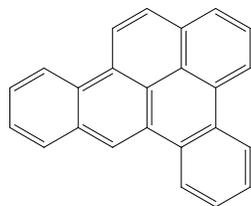
CAS No. 53-70-3

Also known as DB[*a,h*]A**7H-Dibenzo[*c,g*]carbazole**

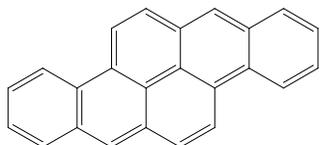
CAS No. 194-59-2

Also known as 7H-DB[*c,g*]C**Dibenzo[*a,e*]pyrene**

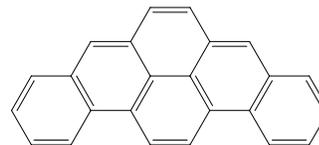
CAS No. 192-65-4

Also known as DB[*a,e*]P**Dibenzo[*a,h*]pyrene**

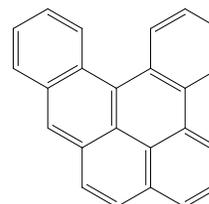
CAS No. 189-64-0

Also known as DB[*a,h*]P**Dibenzo[*a,i*]pyrene**

CAS No. 189-55-9

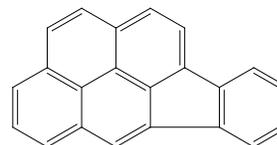
Also known as DB[*a,i*]P**Dibenzo[*a,l*]pyrene**

CAS No. 191-30-0

Also known as DB[*a,l*]P or dibenzo[*def,p*]chrysene**Indeno[1,2,3-*cd*]pyrene**

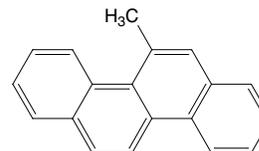
CAS No. 193-39-5

Also known as IP

**5-Methylchrysene**

CAS No. 3697-24-3

Also known as 5-MC

**Carcinogenicity**

The 15 individual PAHs are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals***Benz[a]anthracene***

Benz[a]anthracene caused tumors in mice at several different tissue sites and by several different routes of exposure. *Benz[a]anthracene* administered by stomach tube to adult mice or by subcutaneous injection to newborn mice caused benign or malignant lung tumors (adenoma or adenocarcinoma). Administration by stomach tube also caused liver cancer (hepatocellular carcinoma) in adult mice. *Benz[a]-*

anthracene caused tumors in mice at the site of administration: skin tumors were observed after application to the skin, cancer at the injection site (sarcoma) after subcutaneous injection, and urinary-bladder cancer (carcinoma) after implantation in the bladder (IARC 1973).

Since benz[*a*]anthracene was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified. In newborn mice, intraperitoneal injection of benz[*a*]anthracene caused benign lung tumors (adenoma) in both sexes and benign or malignant liver tumors (adenoma or carcinoma) in males (Levin *et al.* 1984, Wislocki *et al.* 1986, Von Tungeln *et al.* 1999).

Benzo[*b*]fluoranthene

Benzo[*b*]fluoranthene caused tumors in mice by two different routes of exposure. Dermal application of benzo[*b*]fluoranthene caused skin tumors, and subcutaneous injection of benzo[*b*]fluoranthene caused cancer at the injection site (sarcoma) (IARC 1973). Since benzo[*b*]fluoranthene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Benzo[*b*]fluoranthene caused lung cancer (carcinoma) in female rats exposed by intrapulmonary implantation (Deutsch-Wenzel *et al.* 1983). Intraperitoneal injection of benzo[*b*]fluoranthene caused benign lung tumors (adenoma) in male strain A/J mice (a strain with a high spontaneous incidence of lung cancer) (Ross *et al.* 1995, Nesnow *et al.* 1998) and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in newborn male mice (Lavoie *et al.* 1987).

Benzo[*j*]fluoranthene

Dermal exposure to benzo[*j*]fluoranthene caused benign or malignant skin tumors (papilloma or carcinoma) in female mice (IARC 1973). Since benzo[*j*]fluoranthene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Intrapulmonary injection of benzo[*j*]fluoranthene caused lung cancer (squamous-cell carcinoma) in female rats (IARC 1983). In newborn mice, intraperitoneal injection of benzo[*j*]fluoranthene caused benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in both sexes and benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in males (Lavoie *et al.* 1987, 1994).

Benzo[*k*]fluoranthene

Benzo[*k*]fluoranthene caused tumors in two rodent species, at two different tissue sites, and by two different routes of exposure. Intrapulmonary injection of benzo[*k*]fluoranthene caused lung cancer (squamous-cell carcinoma) in female rats, and subcutaneous injection of benzo[*k*]fluoranthene caused cancer at the injection site (sarcoma) in mice of both sexes (IARC 1983).

Benzo[*a*]pyrene

Benzo[*a*]pyrene caused tumors in eight species, including nonhuman primates, at several different tissue sites, and by several different routes of exposure. Benzo[*a*]pyrene had both local and systemic carcinogenic effects and caused tumors after a single dose, after prenatal exposure, and in newborn mice. Benzo[*a*]pyrene caused lung tumors (1) in mice after dietary exposure, prenatal exposure, or subcutaneous or intravenous injection, (2) in rats after administration in the trachea or the bronchus, and (3) in hamsters and nonhuman primates after intratracheal instillation (Andervont and Shimkin 1940, IARC 1973). Oral administration (in the diet or drinking water or by stomach tube) also caused forestomach and esophageal tumors in mice and hamsters, intestinal tumors in hamsters, and mammary-gland tumors in female rats (Horie *et al.* 1965, IARC 1973). Mammary-gland tumors in rats were also observed after intravenous injection. Benzo[*a*]pyrene caused skin tumors in prenatally exposed mice and

in dermally exposed mice, rats, and rabbits. Cancer at the injection site (sarcoma or fibrosarcoma) was observed in mice, rats, hamsters, guinea pigs, newts, monkeys, and nonhuman primates exposed by subcutaneous injection and in mice exposed by intraperitoneal injection (IARC 1973).

Since benzo[*a*]pyrene was listed in the *Second Annual Report on Carcinogens*, numerous additional studies in experimental animals have been identified. These studies reported that benzo[*a*]pyrene caused tumors (1) by additional routes of exposure (including inhalation and other types of injections), (2) in additional species of experimental animals (including fish), and (3) at several additional tissue sites. In studies published since the early 1980s, benzo[*a*]pyrene caused tumors at the following tissue sites:

- The upper respiratory system (mainly the nose and larynx) and upper digestive system (mainly the pharynx, but also the forestomach and esophagus) in male hamsters exposed by inhalation (Thyssen *et al.* 1981).
- Lymphoma in mice exposed by intraperitoneal injection (IARC 2010) or intracolonic injection (Toth 1980, Anderson *et al.* 1983) and in transgenic male and female mice following oral exposure (de Vries *et al.* 1997, Kroese *et al.* 1997).
- The liver in male mice exposed prenatally (Anderson *et al.* 1995) or by intraperitoneal injection (Wislocki *et al.* 1986, Lavoie *et al.* 1987, Rodriguez *et al.* 1997, Von Tungeln *et al.* 1999) and in fish following dietary exposure (Hendricks *et al.* 1985, Hawkins *et al.* 1988), intraperitoneal injection (Hendricks *et al.* 1985), or injection into the fish embryo (transchorionic injection) (Black *et al.* 1988).
- The tongue and larynx (papilloma or carcinoma) in female mice following dietary exposure (Culp *et al.* 1998, Goldstein *et al.* 1998).
- The anus in mice of both sexes exposed by intracolonic injection (Toth 1980).
- The cervix in female mice exposed by intravaginal injection (Näslund *et al.* 1987).

Other studies (not described here) confirmed the earlier findings or found that benzo[*a*]pyrene caused tumors at similar tissue sites in additional species or by additional routes of exposure. Lung tumors were observed following exposure by (1) intratracheal or intrabronchial instillation in female mice (Kim and Lee 1996) and in rabbits of both sexes (Hirao *et al.* 1980), (2) intracolonic injection in female mice (Anderson *et al.* 1983), (3) intrafetal administration in mice of both sexes (Rossi *et al.* 1983), and (4) intrapulmonary injection in rats (Deutsch-Wenzel 1983, Wenzel-Hartung 1990). Intracolonic injection of benzo[*a*]pyrene in mice also caused tumors at tissue sites where it had previously been shown to cause tumors by other routes of exposure: the forestomach, esophagus, mammary gland, and skin (Toth 1980, Anderson *et al.* 1983). Benzo[*a*]pyrene caused forestomach tumors in mice exposed by intraperitoneal injection (Weyand *et al.* 1995), mammary-gland tumors in rats exposed by intramammary injection (Cavaliere *et al.* 1988, 1991), and sarcoma in mice exposed by intraperitoneal injection. Benzo[*a*]pyrene implanted in the buccal cavity caused intestinal tumors in rats (Solt *et al.* 1987), and a single intraperitoneal injection of benzo[*a*]pyrene caused abdominal tumors (mesothelioma and sarcoma) in rats (Roller *et al.* 1992).

Dibenz[*a,h*]acridine

Dibenz[*a,h*]acridine caused tumors in mice at several different tissue sites and by several different routes of exposure. Subcutaneous or intravenous injection of dibenz[*a,h*]acridine caused lung tumors; subcutaneous injection also caused cancer at the injection site (sarcoma), and dermal exposure caused skin tumors (IARC 1973). Since

dibenz[*a,h*]acridine was listed in the *Second Annual Report on Carcinogens*, one study in rats has been identified. Intrapulmonary implantation of pellets containing dibenz[*a,h*]acridine caused lung cancer (carcinoma) in female rats (Deutsch-Wenzel 1983).

Dibenz[*a,j*]acridine

Dibenz[*a,j*]acridine caused tumors in mice at several different tissue sites and by two different routes of exposure. Dermal exposure to dibenz[*a,j*]acridine in mice caused benign or malignant skin tumors (papilloma, carcinoma, or epithelioma). Subcutaneous injection of dibenz[*a,j*]acridine caused cancer at the injection site (sarcoma) in all mouse strains tested and lung tumors in strain A mice (a strain with a high spontaneous incidence of lung cancer) (IARC 1973).

Dibenz[*a,h*]anthracene

Dibenz[*a,h*]anthracene caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of administration. Dibenz[*a,h*]anthracene caused lung tumors in mice after a single intravenous or subcutaneous injection (IARC 1973), in newborn mice after intraperitoneal injection (Buening *et al.* 1979), and in hamsters after intratracheal instillation (Pott *et al.* 1978, as cited in IARC 2010). In mice, oral exposure to dibenz[*a,h*]anthracene caused cancer of the lung (adenomatosis or alveogenic carcinoma) and mammary gland (carcinoma), benign or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma), and tumors of the blood vessels (hemangioendothelioma) (IARC 1973). Exposure to dibenz[*a,h*]anthracene by injection or dermal application also caused local tumors: (1) cancer at the injection site (sarcoma) in rats, guinea pigs, and adult and newborn mice exposed by subcutaneous injection and in pigeons and fowl exposed by intramuscular injection, (2) kidney cancer (adenocarcinoma) in frogs exposed by injection into the kidneys, and (3) benign or malignant skin tumors (papilloma or carcinoma) in mice exposed dermally (IARC 1973).

Since dibenz[*a,h*]anthracene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Lung tumors were observed following administration of dibenz[*a,h*]anthracene by intraperitoneal injection in male strain A/J mice (increased tumor incidence and number of tumors per animal) (Ross *et al.* 1995, Nesnow *et al.* 1996, 1998) and by intrapulmonary implantation in female rats (Wenzel-Hartung *et al.* 1990). Intraperitoneal injection of dibenz[*a,h*]anthracene also caused benign and malignant liver tumors (adenoma and carcinoma) in newborn male mice (Fu *et al.* 1998).

7H-Dibenzo[*c,g*]carbazole

7H-Dibenzo[*c,g*]carbazole caused tumors in several species of experimental animals, at several different tissue sites, and by several different routes of exposure. Administration of 7H-dibenzo[*c,g*]carbazole by stomach tube caused benign and malignant tumors of the liver (hepatocellular adenoma and carcinoma) and forestomach (papilloma and carcinoma) in mice. Administration by intravenous injection or subcutaneous injection caused lung tumors in mice, and administration by intratracheal instillation caused respiratory-system cancer (squamous-cell adenocarcinoma and carcinoma of the bronchus, trachea, and larynx) in hamsters. In mice and rats, administration by subcutaneous injection also caused cancer at the injection site (sarcoma), and dermal application caused benign and malignant skin tumors (papilloma and carcinoma). In a dog, injection of 7H-dibenzo[*c,g*]carbazole into the urinary bladder (intravesicular injection) caused benign and malignant urinary-bladder tumors (transitional-cell papilloma and carcinoma) (IARC 1973).

Since 7H-dibenzo[*c,g*]carbazole was listed in the *Second Annual Report on Carcinogens*, additional studies in mice have been identified, in which additional routes of exposure to 7H-dibenzo[*c,g*]carbazole were reported to cause liver, skin, and lung tumors. Dermal exposure or subcutaneous injection caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) (Warshawsky *et al.* 1994, Mitchell and Warshawsky 1999, Taras-Valero *et al.* 2000), and subcutaneous injection also caused skin tumors (Taras-Valero *et al.* 2000). In male strain A/J mice, a single intraperitoneal injection of 7H-dibenzo[*c,g*]carbazole caused benign lung tumors (adenoma) (Warshawsky *et al.* 1996, Gray *et al.* 2001).

Dibenzo[*a,e*]pyrene

Dibenzo[*a,e*]pyrene caused tumors in mice at two different tissue sites and by two different routes of exposure. Dermal exposure to dibenzo[*a,e*]pyrene caused benign and malignant skin tumors (carcinoma, epithelioma, and papilloma) in females, and subcutaneous injection of dibenzo[*a,e*]pyrene caused cancer at the injection site (sarcoma) in both sexes (IARC 1973).

Dibenzo[*a,h*]pyrene

Dibenzo[*a,h*]pyrene caused tumors in two rodent species, at two different tissue sites, and by several different routes of administration. Dermal exposure to dibenzo[*a,h*]pyrene caused benign and malignant skin tumors (papilloma, sebaceous-gland adenoma, epithelioma, and carcinoma) in mice of both sexes (IARC 1973). Cancer at the site of administration (sarcoma) was observed in mice of both sexes following subcutaneous injection of dibenzo[*a,h*]pyrene and in female rats following subcutaneous implantation of paraffin disks containing dibenzo[*a,h*]pyrene (IARC 1973, Bahna *et al.* 1979).

Since dibenzo[*a,h*]pyrene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Intraperitoneal injection of newborn mice with dibenzo[*a,h*]pyrene caused lung tumors in both sexes and liver tumors in males (Chang *et al.* 1982). In female rats, intramammary injection of dibenzo[*a,h*]pyrene caused cancer of the mammary gland (fibrosarcoma or adenocarcinoma) (Cavalieri *et al.* 1989), and subcutaneous injection caused cancer at the injection site (sarcoma) (Bahna *et al.* 1979).

Dibenzo[*a,i*]pyrene

Dibenzo[*a,i*]pyrene caused tumors in two rodent species, at two different tissue sites, and by several different routes of administration. Dermal exposure to dibenzo[*a,h*]pyrene caused benign or malignant skin tumors (papilloma or epithelioma) in mice, and subcutaneous injection caused cancer at the injection site (sarcoma) in mice and hamsters (IARC 1973).

Since dibenzo[*a,i*]pyrene was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Intraperitoneal injection of newborn mice with dibenzo[*a,i*]pyrene caused lung tumors in both sexes and liver tumors in males (Chang *et al.* 1982), and intratracheal instillation caused respiratory-system cancer (mostly squamous-cell carcinoma, but also adenocarcinoma and anaplastic carcinoma) in hamsters of both sexes (Sellakumar and Shubik 1974, Stenbäck and Sellakumar 1974). Dibenzo[*a,i*]pyrene administered by intramammary injection caused cancer of the mammary gland (fibrosarcoma and adenocarcinoma) in female rats (Cavalieri *et al.* 1989).

Dibenzo[*a,l*]pyrene

Dibenzo[*a,l*]pyrene caused tumors in mice at two different tissue sites and by two different routes of exposure. Subcutaneous injection of dibenzo[*a,l*]pyrene caused cancer at the injection site (sarcoma) in

mice of both sexes (IARC 1973), and dermal exposure caused skin tumors in female mice (IARC 1983).

Since dibenzo[*a,l*]pyrene was listed in the *Fifth Annual Report on Carcinogens*, additional studies in experimental animals have been identified, which reported that dibenzo[*a,l*]pyrene caused tumors (1) by additional routes of exposure (oral, prenatal, and intraperitoneal injection), (2) in additional species of experimental animals (rats, hamsters, and fish), and (3) at additional tissue sites, including sites distant from the route of administration. Administration of dibenzo[*a,l*]pyrene by stomach tube to female mice caused ovarian tumors (predominately granulosa) (Buters *et al.* 2002). Dietary administration of dibenzo[*a,l*]pyrene to fish caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma or cholangiocellular adenoma) and benign tumors of the stomach (papillary adenoma) and swim bladder (papillary adenoma) (Reddy *et al.* 1999a,b). Intraperitoneal injection of dibenzo[*a,l*]pyrene caused lung tumors in strain A/J mice (Pralhad *et al.* 1997). Lung and liver tumors were observed in prenatally exposed mice (Yu *et al.* 2006) and in newborn mice exposed by intraperitoneal injection (Platt *et al.* 2004); lung tumors occurred in both sexes, and liver tumors in males. In addition, prenatal exposure to dibenzo[*a,l*]pyrene caused T-cell lymphoblastic lymphoma in mice of both sexes (Yu *et al.* 2006). Local tumors also were observed in rats and hamsters: intramammary injection of dibenzo[*a,l*]pyrene caused mammary-gland cancer (adenocarcinoma or fibrosarcoma) in female rats (Cavalieri *et al.* 1989, 1991), and application of dibenzo[*a,l*]pyrene directly to the tongue caused cancer of the oral cavity (squamous-cell carcinoma) in female hamsters (Schwartz *et al.* 2004).

Indeno[1,2,3-*cd*]pyrene

Indeno[1,2,3-*cd*]pyrene caused tumors in mice at two different tissue sites and by two different routes of exposure. Dermal exposure to indeno[1,2,3-*cd*]pyrene caused benign and malignant skin tumors (papilloma and carcinoma) in females, and subcutaneous injection caused cancer at the injection site (sarcoma) in males (IARC 1973). Since indeno[1,2,3-*cd*]pyrene was listed in the *Second Annual Report on Carcinogens*, an additional study in rodents has been identified. Intrapulmonary administration of indeno[1,2,3-*cd*]pyrene caused lung cancer (carcinoma) in female rats (Deutsch-Wenzel 1983).

5-Methylchrysene

5-Methylchrysene caused tumors in mice at two different tissue sites and by two different routes of exposure. Dermal exposure to 5-methylchrysene caused skin cancer (carcinoma) in females, and subcutaneous injection caused cancer at the injection site (sarcoma) in males (IARC 1983). Since 5-methylchrysene was listed in the *Fifth Annual Report on Carcinogens*, additional studies in mice have been identified. Intraperitoneal injection of 5-methylchrysene caused lung tumors in male strain A mice (Ross *et al.* 1995, Nesnow *et al.* 1998) and lung and liver tumors in newborn mice of both sexes (Hecht *et al.* 1985, el-Bayoumy *et al.* 1989).

Studies on Mechanisms of Carcinogenesis

Most PAHs with potential biological activity range in size from two to six fused aromatic rings (IARC 2010). Because of the vast range in molecular weight of PAHs, several of the physicochemical properties that are critical to their biological activity also vary greatly. Five properties in particular have a decisive influence on the biological activity of PAHs: their vapor pressure, their adsorption on surfaces of solid carrier particles, their absorption into liquid carriers, their lipid-aqueous partition coefficient in tissues, and their limits of solubility in the lipid and aqueous phases of tissues. These properties are inti-

mately linked with the metabolic activation of the most toxic PAHs, and an understanding of the nature of this interaction helps in the understanding of their deposition and disposition. It has been proposed that PAHs share a similar mechanism of carcinogenic action. In general, PAHs are converted to oxides and dihydrodiols, which in turn are oxidized to diol epoxides. Both oxides and diol epoxides are ultimate DNA-reactive metabolites. PAH oxides can form stable DNA adducts, and diol epoxides can form stable and depurinating adducts with DNA through formation of electrophilic carbonium ions. Most of the 15 listed PAHs have been shown to be initiators of skin cancer (IARC 1983, 2010). The International Agency for Research on Cancer concluded that benzo[*a*]pyrene was carcinogenic to humans based on data on the mechanism of carcinogenicity (IARC 2010).

Cancer Studies in Humans

No epidemiological studies on exposure to the individual PAHs were identified. Individual PAHs are found in the environment not in isolation but as components of highly complex mixtures of chemicals. PAHs are very widespread environmental contaminants, because they are formed during incomplete combustion of materials such as coal, oil, gas, wood, or garbage or during pyrolysis of other organic material, such as tobacco or charbroiled meat. Data on the carcinogenicity of PAHs in humans are available only for mixtures containing PAHs. It is difficult to ascertain the carcinogenicity of the component PAHs in these mixtures because of potential chemical interactions and the presence of other carcinogenic substances in the mixtures. In 2005, IARC reevaluated PAHs. Although certain occupations with high PAH exposure (e.g., coal gasification and coke production) were classified as carcinogenic in humans, the roles of individual PAHs could not be defined (IARC 2010).

Properties

Three of the listed PAHs (dibenz[*a,h*]acridine, dibenz[*a,i*]acridine, and 7*H*-dibenzo[*c,g*]carbazole) contain a nitrogen atom as part of a ring and therefore are classified as heterocyclic PAHs. The PAHs can exist as leaflets, plates, needles, or at room temperature and range in color from colorless to yellow, green or blue. All PAHs are soluble in water and slightly soluble in ethanol, acetone or acid; most are soluble in benzene. Physical and chemical properties of the 15 PAHs are listed in the table below. In addition to the properties listed in the table, benzo[*a*]pyrene has a specific gravity of 1.351 and a vapor density relative to air of 8.7, and dibenzo[*a,h*]anthracene has a specific gravity of 1.282 (HSDB 2009).

Use

IARC (1983) reported that no commercial uses or applications were known for dibenzo[*a,h*]pyrene, dibenzo[*a,i*]pyrene, and 5-methylchrysene. The remaining twelve listed PAHs are used only in biochemical, biomedical, laboratory, or cancer research (HSDB 2009). At least five of the listed PAHs are present in coal tar, which is used as a fuel in the steel industry in open-hearth and blast furnaces (HSDB 2009). Coal tar is also used in the clinical treatment of skin disorders such as eczema, dermatitis, and psoriasis. Coal tar is distilled to produce a variety of products, including coal-tar pitch and creosote. At least two of the listed PAHs are present in coal-tar pitch, which is used primarily as a binder for aluminum smelting electrodes in the aluminum reduction process. Coal-tar pitch is also used in roofing, in surface coatings, for pitch-coke production, and for a variety of other applications (IARC 1985). At least two of the listed PAHs are found in creosote, which is used to preserve railroad ties, marine pilings, and telephone poles. Some creosote is used for fuel by steel producers (NIOSH 1977). At least three of the listed PAHs are pres-

PAH	Physical form	MW ^a	MP (°C) ^a	BP (°C) ^a	Log K_{ow} ^b	Sol. at 25°C (g/L) ^b	VP at 25°C (mm/Hg) ^b
BA	colorless leaflets or plates with greenish-yellow fluorescence	228.3	160	437.6	5.79	9.4×10^{-6}	2.1×10^{-7}
B[b]F	colorless needles	252.3	168	NR	5.78	$1.2 \times 10^{-6a,c}$	5.0×10^{-7}
B[j]F	orange needles or yellow plates	252.3	166	NR	6.11	2.5×10^{-6c}	2.62×10^{-8}
B[k]F	pale-yellow needles	252.3	217	480	6.84 ^a	8.0×10^{-7}	9.7×10^{-10}
B[a]P	pale-yellow needles	252.3	179 to 179.3	310 to 312 at 10 mm Hg	5.97	1.62×10^{-6}	5.49×10^{-9a}
DB[a,h]AC	yellow crystals	279.4	226 ^b	NR	5.73	1.59×10^{-3}	1.85×10^{-9}
DB[a,i]AC	yellow needles or prisms	279.4	216	NR	5.63	1.8×10^{-5}	1.85×10^{-9}
DB[a,h]A	colorless leaflets, plates, or crystals	278.3	266	524	6.5 ^a	2.49×10^{-6}	1.0×10^{-10}
7H-DB[c,g]C	needles	267.3	158	NR	5.58	6.3×10^{-5c}	3.4×10^{-9}
DB[a,e]P	pale-yellow to yellow-red needles	302.4	233.5	NR	7.28	8.02×10^{-8}	7.03×10^{-11}
DB[a,h]P	yellow plates	302.4	317	NR	7.28	3.5×10^{-8}	6.41×10^{-12}
DB[a,i]P	greenish-yellow needles, prisms, or lamellae	302.4	280	275 at 0.05 mm Hg	7.28	5.54×10^{-7}	1.78×10^{-11}
DB[a,l]P	yellow plates	302.4	162.4	NR	7.71 ^a	3.6×10^{-7}	4.8×10^{-10}
IP	yellow plates	276.3	163.6	536	6.7	1.9×10^{-7}	1.25×10^{-10}
5-MC	needles with brilliant bluish-violet fluorescence in UV light.	242.3	117.5	NR	6.07	6.2×10^{-5a}	2.53×10^{-7}

Sources: ^aHSDDB 2009 except as indicated. ^bChemIDplus 2009 except as indicated. ^cTemperature not specified. MW = molecular weight. MP = melting point. BP = boiling point. Sol = water solubility. VP = vapor pressure. NR = not reported.

ent in bitumens and asphalt, which are used for paving roads, sound- and water-proofing, and coating pipes.

Production

PAHs are not produced for commercial use in the United States (IARC 1983, HSDDB 2009). Production data for tar, tar pitch, creosote, mineral oils, and coke, which contain various PAHs, are included in their respective profiles in the Report on Carcinogens (see Coal Tars and Coal-Tar Pitches, Coke-Oven Emissions, and Mineral Oils: Untreated and Mildly Treated).

Exposure

PAHs are ubiquitous in the environment, and the general population is exposed to measurable background levels (IPCS 1998). Sources of PAHs in ambient air (both outdoors and indoors) include forest fires, volcanoes, industrial emissions, residential and commercial heating with wood, coal, or other biomass fuels (oil and gas heating produce much lower quantities of PAHs), motor-vehicle exhaust (especially diesel), and other indoor sources such as cooking and tobacco smoke (IARC 1983, IPCS 1998). Food is a major source of exposure to PAHs for the general population (IPCS 1998). Skin contact with PAH-contaminated soils and the use of dermally applied pharmaceutical products based on coal tar also have been identified as sources of exposure for the general population (Jongeneelen *et al.* 1985, Viau and Vyskocil 1995, IPCS 1998, Jongeneelen 2001).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, industrial releases of PAHs to the environment peaked in 2000, when over 4.9 million pounds was released, mostly to on-site and off-site landfills and to air. Releases have been relatively stable at a lower level since 2002. In 2008, 1,192 facilities released over 1.2 million pounds of PAHs to air, water, or on- or off-site landfills (mostly to air or landfills) (TRI 2010).

In the past, benzo[a]pyrene often was used as a marker for measuring exposure to PAHs. However, it is now possible or even common to measure many PAHs individually. Mean concentrations of individual PAHs in ambient urban air usually range from 1 to 30 ng/m³ (IPCS 1998). The concentrations of PAHs in the air during winter, when residential heating is a major source, generally are at least an order of magnitude higher than those in summer (IPCS 1998). Areas near sources such as motor-vehicle traffic also have higher air concentrations of PAHs. For individuals who smoke, mainstream

tobacco smoke is a major source of exposure to PAHs. Concentrations of total PAHs in mainstream smoke ranged from 1 to 1.6 µg/cigarette. Sidestream smoke is a major source of PAHs in indoor air. Concentrations of benzo[a]pyrene in sidestream smoke ranged from 52 to 95 ng/cigarette — more than three times the concentration in mainstream smoke.

PAHs in water may originate from surface runoff (e.g., from the erosion of asphalt pavement or from air deposition of smaller particles) (IPCS 1998). Industrial effluents also can contribute to PAH concentrations in surface waters. However, concentrations of PAHs in water usually are very low, because of their low solubility. Surface-water concentrations typically do not exceed 50 ng/L; higher concentrations are found in more contaminated areas. PAH concentrations are higher in rainwater than in surface waters (100 to 200 ng/L, with some samples exceeding 1,000 ng/L). Because PAHs have very high octanol-water partition coefficients (log K_{ow}), they bind tightly to soil particles and are relatively immobile in soil; therefore, concentrations in groundwater and drinking water typically are very low (0.02 to 1.8 ng/L), and concentrations of PAHs in sediment may be very high, ranging up to several thousand micrograms per kilogram.

Estimates of daily PAH intake from food vary widely, ranging from a few nanograms to a few micrograms per person. Sources of PAHs in the diet include barbecued, grilled, broiled, and smoke-cured meats; roasted, baked, and fried foods (prepared by high-temperature processing); breads, cereals, and grains (at least in part from gas or flame drying of grains); and vegetables grown in contaminated soil or with surface contamination from atmospheric deposition of PAHs (IARC 1983, IPCS 1998, JECFA 2005). The Joint United Nations Food and Agriculture Organization–World Health Organization Expert Committee on Food Additives and Contaminants determined a representative mean daily human intake of benzo[a]pyrene to be 4 ng/kg of body weight and a high-end daily human intake of total PAHs to be 10 ng/kg (JECFA 2005). Among common foods, the highest PAH levels were found in grilled or barbecued steak, chicken with skin and bones, and hamburgers, especially when “well done” or “very well done” (Larsson *et al.* 1983, Lijinsky 1991, Lodovici *et al.* 1995, Kazerouni *et al.* 2001). Because PAHs form on or near the surface of meat, rather than in the interior, foods that are cooked to the same degree without being exposed to flames do not show significant levels of PAHs. However, a study of PAHs in the Italian diet indicated a total PAH concentration of about 4 ng/g in fried beef (Lodovici *et al.*

1995) and benzo[*a*]pyrene concentrations of up to about 4 ng/g in well-done grilled meat. PAHs are also introduced by certain methods of preserving meat and other food products (Lijinsky 1991). In foods smoked in traditional smoking kilns, the average concentration was 1.2 µg/kg for benzo[*a*]pyrene and 9 µg/kg for total PAHs, compared with 0.1 µg/kg for benzo[*a*]pyrene and 4.5 µg/kg for total PAHs in foods treated in a modern kiln (Guillen 1994).

Accumulation of PAHs in foods of animal origin, especially livestock, is due mainly to the consumption of contaminated feed (Ramesh *et al.* 2004). Unprocessed foods such as vegetables, fruits, vegetable oils, dairy products, and seafood can be contaminated with PAHs by deposition of particles and vapors from the atmosphere and uptake from soil, water, and sediment (Roth *et al.* 1998, Ramesh *et al.* 2004). PAH levels are low in cereals and beans, but drying techniques used for preservation, such as combustion gas heating and smoking, increase concentrations of PAHs in these foods. Eggs and dairy products such as cheese, milk, and butter contain low levels of PAHs. Consumption of seafood, especially bottom-feeding shellfish and finfish, may contribute considerably to the amount of PAHs in the diet. Species near the top of the food chain, such as humans, do not bioaccumulate PAHs, because of their higher capacity to metabolize PAHs (Ramesh *et al.* 2004).

A specific urinary metabolite of pyrene, 1-hydroxypyrene, has been suggested as a biomarker of human exposure to PAHs (Jongeneelen *et al.* 1985, Jongeneelen 2001). In representative samples from the general population, 1-hydroxypyrene has been detected in the urine of nearly all individuals, at median concentrations typically less than 0.1 µmol/mol of creatinine (Huang *et al.* 2004). The National Health and Nutrition Examination Survey analysis of 2,312 urine samples collected from the U.S. general population in 1999 to 2000 found a geometric mean concentration of 1-hydroxypyrene of 0.039 µmol/mol of creatinine (95% CI = 0.034 to 0.046 µmol/mol). The level for adult smokers was three times that for nonsmokers (geometric mean = 0.080 vs. 0.025 µmol/mol). These data are comparable with other recent data on non-occupationally exposed populations in Europe and Canada.

Occupational exposure to PAHs is primarily through inhalation and dermal contact. Industrial processes that involve the pyrolysis or combustion of coal and the production and use of coal-derived products, including coal tar and coal-tar-derived products, are major sources of occupational exposure to PAHs. Workers in coal-tar production plants, coking plants, bitumen and asphalt production plants, coal-gasification sites, smoke houses, aluminum-production plants, coal-tarring facilities, and municipal trash incinerators are exposed to PAHs. Exposure may also result from inhaling engine exhaust and using products that contain PAHs in a variety of other industries, such as mining, oil refining, metalworking, chemical production, transportation, and the electrical industry (Vanrooij *et al.* 1992). Studies in Germany measured concentrations of PAHs in the breathing zone of chimney sweeps during so-called “black work”; the PAHs in the air samples varied depending on the type of fuel burned (oil, oil/solid, or solid) (Knecht *et al.* 1989). Specific occupational exposure to coal tar, coal-tar pitch, creosote, mineral oils, and coke that contain various PAHs is described in the profiles for these substances (see Coal Tars and Coal-Tar Pitches, Coke Oven Emissions, and Mineral Oils). Concentrations of PAHs in coal-tar products may range from less than 1% to 70% or more (ATSDR 2002). Occupational exposure can lead to PAH body burdens among exposed workers that are considerably higher than those in the general population. There is growing awareness that uptake of PAHs through the skin is substantial (Jongeneelen 2001). Dermal uptake has been shown to contribute to the internal exposure of workers to PAHs; a study in the creosote industry

found that the total internal dose of PAHs did not necessarily correlate with inhalation-exposure levels alone, and that dermal exposure contributed significantly (Vanrooij *et al.* 1992).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Polycyclic organic matter is listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Polycyclic organic matter is listed as a hazardous air pollutant.

Urban Air Toxics Strategy: Polycyclic organic matter is identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Polynuclear aromatic hydrocarbons are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.0038 µg/L for benzo[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, dibenzo[*a,h*]anthracene, and indeno[1,2,3-*cd*]pyrene; based on fish or shellfish consumption only = 0.018 µg/L for benzo[*a*]anthracene, benzo[*a*]pyrene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, dibenzo[*a,h*]anthracene, and indeno[1,2,3-*cd*]pyrene.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = ranges from 1 lb to 5,000 lb for the various PAHs.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: All 15 PAHs are listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of specific PAHs = U018, U022, U063, U064, U137.

Numerous specific PAHs are listed as hazardous constituents of waste.

Safe Drinking Water Act

Maximum contaminant level = 0.0002 mg/L for benzo[*a*]pyrene.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.0002 mg/L for benzo[*a*]pyrene.

Limits on PAH levels in various color additives are prescribed in 21 CFR 74 and 178.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible for benzo[*a*]anthracene, benzo[*b*]fluoranthene, and benzo[*a*]pyrene.

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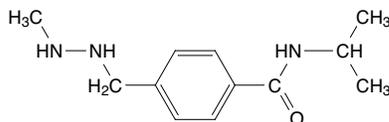
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Procarbazine and Its Hydrochloride

CAS Nos. 671-16-9 and 366-70-1

Reasonably anticipated to be human carcinogens

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

Procarbazine and procarbazine hydrochloride are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals. The names “procarbazine” and “procarbazine hydrochloride” are used interchangeably in published studies; because only procarbazine hydrochloride is produced, it has been assumed that procarbazine hydrochloride was the substance under study.

Cancer Studies in Experimental Animals

Exposure to procarbazine hydrochloride by intraperitoneal injection caused tumors in rats and mice at several different tissue sites. In both rats and mice, it caused cancer of the brain (olfactory neuroblastoma) and hematopoietic system (lymphoma in rats and lymphoma or leukemia in mice). In rats, it also caused mammary-gland cancer (adenocarcinoma) in both sexes. In mice, it also caused benign lung tumors (adenoma) in both sexes and uterine cancer (adenocarcinoma) in females (NCI 1979).

Since procarbazine hydrochloride was listed in the *Second Annual Report on Carcinogens*, it has been reviewed several times by the International Agency for Research on Cancer, which identified additional studies in experimental animals. Administration of procarbazine hydrochloride by stomach tube caused tumors at some of the same tissue sites observed for intraperitoneal injection: leukemia and benign lung tumors (adenoma) in mice of both sexes and mammary-gland cancer (carcinoma or adenocarcinoma) in female rats. In other studies in rats, transplacental exposure caused cancer of neural tissue (neurinoma), and administration by intravenous injection caused tumors in various organs (mainly kidney tumors and intra-abdominal spindle-cell sarcoma). In rhesus and cynomolgus monkeys, exposure to procarbazine hydrochloride by several routes (orally or by intraperitoneal, subcutaneous, or intravenous injection) resulted in the development of acute myelogenous leukemia or lymphoma, blood-vessel cancer (hemangiosarcoma in the kidney), and bone cancer (osteosarcoma) in both sexes of both species (IARC 1981, 1982, 1987).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to procarbazine hydrochloride. Procarbazine is used mainly in combination with other chemotherapeutic agents for the treatment of Hodgkin's lymphoma; it has been used historically in combination chemotherapy with mechlorethamine (nitrogen mustard), Oncovin (vincristine), and prednisone (MOPP) and more recently with other chemotherapeutic agents. MOPP was associated with acute nonlymphocytic leukemia in a number of studies (IARC 1981); however, these studies did not permit conclusions to be drawn about the independent effects of procarbazine and nitrogen mustard.

Since procarbazine hydrochloride was listed in the *Second Annual Report on Carcinogens*, additional studies in humans have been identified. In most cases, nitrogen mustard (nitrogen mustard hydrochloride), which is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*, or its derivative melphalan, which is listed as *known to be a human carcinogen*, also was administered (IARC 1987). Some studies reported increased risks of secondary hematologic cancer after treatment with various procarbazine-containing regimens that did not include nitrogen mustard or melphalan (Tucker *et al.* 1988, Kaldor *et al.* 1990, Hoppe 1992, Schellong *et al.* 1997, Brusamolino *et al.* 1998), but the independent effect of procarbazine could not be evaluated. However, in a large case-control study, procarbazine (but not nitrogen mustard) was associated with significantly increased risks of leukemia and cancer of the bones, joints, cartilage, and soft tissues in models adjusting for exposure to other drugs (Boice *et al.* 1995). No association between procarbazine treatment and breast-cancer risk was observed among women with secondary breast cancer following treatment for Hodgkin's lymphoma (Travis *et al.* 2003, 2005).

Properties

Procarbazine hydrochloride is a methylhydrazine derivative (NCI 1979) that exists at room temperature as a white to pale-yellow crystalline powder with a slight odor. It is soluble in water, methanol, chloroform, and diethyl ether and is sensitive to oxidation (IARC 1981). Physical and chemical properties of procarbazine hydrochloride are listed in the following table.

Property	Information
Molecular weight	257.8 ^a
Melting point	223°C ^b
Log <i>K</i> _{ow}	-1.69 ^a
Water solubility	29.4 g/L at 25°C ^a
Vapor pressure	1.01 × 10 ⁻¹¹ mm Hg at 25°C ^a

Sources: ^aChemIDplus 2009, ^bAkron 2009.

Use

Procarbazine hydrochloride is used in human medicine as an anti-neoplastic and chemotherapeutic agent. It is used in combination with other antineoplastic agents such as nitrogen mustard, vincristine, and prednisone to treat Hodgkin's disease. In the MOPP regimens, the recommended dose for adults is 100 mg/m² for 10 to 14 days (IARC 1981).

Production

In 2009, procarbazine hydrochloride was produced by two U.S. manufacturers (HSDB 2009). Three U.S. suppliers were identified for procarbazine hydrochloride and one U.S. supplier for procarbazine (ChemSources 2009). No other data on U.S. production, imports, or exports of procarbazine hydrochloride were found. Procarbazine hydrochloride is the active ingredient in one pharmaceutical product approved by the U.S. Food and Drug Administration (FDA 2009).

Exposure

The routes of potential human exposure to procarbazine hydrochloride are ingestion, inhalation, and dermal contact (HSDB 2009). For patients receiving procarbazine hydrochloride as a chemotherapeutic agent, the typical initial dose of is 2 to 4 mg/kg of body weight daily, given orally in divided doses for 1 week, then 4 to 6 mg/kg daily until signs of bone-marrow depression occur. After bone-marrow recovery, treatment is resumed at a daily dose of 1 to 2 mg/kg (IARC 1981).

Occupational exposure to procarbazine hydrochloride could occur during manufacture, formulation, or packaging of the drug product. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,328 workers, including 289 women, potentially were exposed to procarbazine hydrochloride (NIOSH 1990). Health professionals, such as physicians, nurses, and pharmacists, and service workers, such as housekeepers, potentially are exposed to procarbazine hydrochloride during drug preparation, administration, and cleanup.

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Procarbazine hydrochloride is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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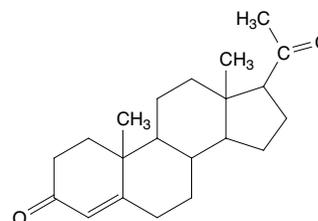
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Progesterone

CAS No. 57-83-0

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

Progesterone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Progesterone caused tumors of the mammary gland and female genital tract in several species of experimental animals. In female mice, progesterone administered by subcutaneous implantation increased the incidence of mammary-gland cancer (carcinoma) and caused its

earlier onset, as well as causing tumors of the ovary (granulosa-cell tumors) and uterus (endometrial sarcoma). Administration of progesterone to newborn female mice by subcutaneous injection caused mammary-gland tumors and tumors of the genital tract, especially the vagina and cervix. In female dogs, long-term intramuscular injection of progesterone caused benign mammary-gland tumors (papilloma and adenoma) (IARC 1974b, 1979, 1982).

Progesterone administered in combination with other chemicals (known carcinogens) had similar effects. In female mice infected with mammary tumor virus, subcutaneous injection of progesterone increased the incidence of mammary-gland tumors induced by 3-methylcholanthrene; in uninfected mice, it caused earlier onset of tumors. In ovariectomized mice given 3-methylcholanthrene via intrauterine implantation, subcutaneous injection of progesterone promoted the development of uterine tumors (endometrial sarcoma). Subcutaneous implantation of progesterone together with local application of 3-methylcholanthrene caused vaginal and cervical cancer (squamous-cell carcinoma) in female mice. In rats, subcutaneous or intramuscular injection of progesterone following exposure to 7,12-dimethylbenz[*a*]anthracene or 3-methylcholanthrene resulted in increased incidence and/or earlier onset of mammary-gland tumors. In female rats administered 2-acetylaminofluorene in the diet, intramuscular injection of progesterone promoted the development of mammary-gland tumors (IARC 1974b, 1979, 1982).

Cancer Studies in Humans

At the time progesterone was listed in the *Fourth Annual Report on Carcinogens*, no epidemiological studies were available that evaluated the relationship between human cancer and exposure specifically to progesterone. Since that time, several additional epidemiological studies have been identified. These studies focused primarily on progesterone-only oral contraceptives or estrogen-progesterone combinations used as oral contraceptives or menopausal therapies. Relatively few studies have addressed the more limited use of progesterone as an injectable or implanted contraceptive or in treatment of other medical conditions (e.g., for amenorrhea, uterine bleeding or fibroma, or pregnancy complications or in certain infertility drugs).

The International Agency for Research on Cancer (IARC 1999) evaluated a number of cohort and case-control studies of cancer risk, principally of breast and endometrial cancer, associated with the use of progestogen-only contraceptives, and concluded that there was inadequate evidence of the carcinogenicity of progestogen-only contraceptives in humans. A subsequent review by La Vecchia and Franceschi (2002) supported these findings. However, a more recent case-control study reported an increased risk of breast cancer with prolonged use of progesterone contraceptives in premenopausal women over 40 years of age (Fabre *et al.* 2007). No other studies of progesterone-only contraceptives were identified.

Estrogens (steroidal) are listed in the Report on Carcinogens as *known human carcinogens*; it is difficult to distinguish the independent or interactive carcinogenic effects of progestogens and estrogens when they are used in combination. IARC evaluated the carcinogenicity of estrogen-progestogen combinations used as contraceptives and for menopausal therapy, concluding that (1) there was sufficient evidence of the carcinogenicity of oral contraceptives in humans based on increased risks of breast cancer among current and recent users only, of cancer of the cervix, and of liver cancer, and (2) sufficient evidence of the carcinogenicity of combined estrogen-progestogen menopausal therapy in humans based on increased risk of breast cancer (IARC 2007, Grosse *et al.* 2009). IARC concluded that the risk of endometrial cancer associated with menopausal therapy decreased with increasing duration of progestogen use.

One small case-control study of breast-cancer risk among women receiving infertility drugs, some of which contained progesterone, was identified; the study included 8 cases (Jensen *et al.* 2007). A significant threefold increase in risk associated with progesterone was found; however, all of these women had also received other drugs.

Properties

Progesterone is a steroid hormone that is an odorless white crystalline powder at room temperature. It is practically insoluble in water, sparingly soluble in vegetable oils, and soluble in acetone, alcohol, dioxane, and concentrated sulfuric acid. It is sensitive to light, but stable in air (IARC 1979). Physical and chemical properties of progesterone are listed in the following table.

Property	Information
Molecular weight	314.5 ^a
Specific gravity	1.166 at 23°C ^a
Melting point	127°C to 131°C ^a
Log <i>K</i> _{ow}	3.87 ^a
Water solubility	0.00881 g/L at 25°C ^a
Vapor pressure	1.3 × 10 ⁻⁶ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Progesterone is a naturally occurring steroidal hormone found in a wide variety of tissues and biological fluids. It is secreted by the ovary in normal adult cycling female mammals, by the placenta in pregnant females, and by the adrenal cortex. It is essential for the normal functioning of the uterine lining, for the development of mammary glands, and for support of pregnancy through parturition (Prosser 1973). Progesterone is used in medicine to treat secondary amenorrhea, and dysfunctional uterine bleeding and in combination hormone-replacement therapies (MedlinePlus 2009). It has also been used to treat female hypogonadism, dysmenorrhea and premenstrual tension, habitual and threatened abortion, preeclampsia and toxemia of pregnancy, mastodynia, uterine fibroma, and neoplasms of the breast and endometrium (IARC 1979, HSDB 2009). Progesterone embedded in an intrauterine device is used for contraception (FDA 2009). In veterinary medicine, progesterone has been used to control habitual abortion and to delay estrus and ovulation in cattle, swine, and dogs. It is also used to improve weight gain and feed efficiency in animals (IARC 1979).

Production

Progesterone is a naturally occurring steroid hormone produced endogenously by all mammalian species. Daily production in humans ranges from 0.8 mg in men to 26 mg in adult women with normal menstrual cycles (IARC 1974a). Before the U.S. government imposed restrictions in 1973, estimated total annual U.S. sales of progesterone for use in human medicine were less than 110 lb (IARC 1974b). In 1975, U.S. production of 13 estrogen and progestin substances, including progesterone, amounted to 23,100 lb (IARC 1979). One U.S. commercial producer of progesterone was identified in 2009 (SRI 2009), and progesterone was available from 36 U.S. suppliers in 2010 (Chem Sources 2010). U.S. imports of progesterone of animal or vegetable origin were 26,400 lb in 2001, the last year these products were imported (USITC 2009).

Exposure

The primary routes of potential exogenous human exposure to progesterone are ingestion, injection of medications containing progesterone, implantation, dermal contact, and inhalation. The U.S. Food and Drug Administration has approved 26 products containing pro-

gesterone as an active ingredient for use in the United States (FDA 2009). These medications are available as tablets (12), injectables (9), capsules (2), vaginal gels (2), or vaginal inserts (1). A limited segment of the population is exposed to progesterone embedded in intrauterine contraceptive devices. Embedded systems release progesterone at an average daily rate of 65 µg for one year, via membrane-controlled diffusion (Mosby 2001). Progesterone capsules come in doses of 100 and 200 mg of micronized progesterone. Vaginal gel applicators deliver 45 mg (4% gel) or 90 mg (8% gel) of progesterone (FDA 2009). Human placental extracts, of which progesterone is believed to be the main constituent, have been used in preparations for cosmetic use (at concentrations of 0.1% to 1.0%), hair conditioners, shampoos, and grooming-aid tonics (at < 0.1%) (IARC 1979). Consumers could be dermally exposed to progesterone through use of these products.

In 1977, the FDA reported that progesterone was found in cow's milk at concentrations of 1 to 30 ng/mL and in milk products at up to 300 µg/kg (in butter). It was also detected as a natural constituent in certain plant species. The meat from animals treated with progesterone implants may contain progesterone at an average concentration of 0.33 mg/kg. Consumers could potentially be exposed to progesterone by ingesting these food products (IARC 1979).

Potential occupational exposure to progesterone may occur through inhalation and dermal contact during its production or formulation into pharmaceuticals. A joint investigation of an oral contraceptive manufacturing facility conducted by the National Institute for Occupational Safety and Health and the Centers for Disease Control and Prevention found evidence of hyperestrogenism in both male and female workers and wide variations in air-sample concentrations of estrogen and progesterone (Mills *et al.* 1984). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 287 workers, including 55 women, potentially were exposed to progesterone (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Food and Drug Administration (FDA)

Progesterone is a prescription drug subject to labeling and other requirements. Maximum levels of progesterone in edible animal tissues are prescribed in 21 CFR 556.540. Progesterone in topically applied hormone-containing drugs for over the counter use is no longer considered generally recognized as safe and effective.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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1,3-Propane Sultone

CAS No. 1120-71-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)



Carcinogenicity

1,3-Propane sultone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

1,3-Propane sultone caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Administration of 1,3-propane sultone to rats by stomach tube caused brain cancer (glioma of the cerebrum and cerebellum) in both sexes and mammary-gland cancer (adenocarcinoma) in females. The incidences of leukemia and cancer of the small intestine (adenocarcinoma) and ear duct (squamous-cell carcinoma) also were somewhat increased in rats of both sexes (IARC 1974, Weisburger *et al.* 1981). In rats of unspecified sex given weekly or single intravenous injections of 1,3-propane sultone, tumors were observed at various tissue sites, including the brain and nervous system. A single intravenous injection of 1,3-propane sultone to pregnant rats on the 15th day of gestation caused malignant neural tumors and tumors of the pancreas and ovary in the offspring. 1,3-Propane sultone administered by subcutaneous injection caused cancer at the injection site in female mice

following repeated injections (adenocanthoma and sarcoma) and in rats (of unspecified sex) following single or repeated injections (myosarcoma, fibrosarcoma, or sarcoma) (IARC 1974).

Since 1,3-propane sultone was listed in the *Fourth Annual Report on Carcinogens*, additional studies in rodents have been identified. Dermal exposure to 1,3-propane sultone caused tumors of the skin and lymphoreticular tissue in mice of both sexes, and subcutaneous injection of 1,3-propane sultone caused lung cancer (anaplastic adenocarcinoma) in male rats (IARC 1999).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1,3-propane sultone.

Properties

1,3-Propane sultone exists at room temperature as a colorless liquid or white crystalline solid (Akron 2009, HSDB 2009). In liquid form (at temperatures above 31°C), it has a foul odor. It is very soluble in water and readily soluble in ketones, esters, and aromatic hydrocarbons. It is stable under normal handling and storage conditions, but it may react slowly with water to form an acid compound, 3-hydroxy-1-propanesulfonic acid. When heated to decomposition, 1,3-propane sultone emits toxic fumes of sulfur oxides and carbon monoxide. Physical and chemical properties of 1,3-propane sultone are listed in the following table.

Property	Information
Molecular weight	122.1 ^a
Specific gravity	1.393 at 40°C/4°C ^a
Melting point	31°C ^a
Boiling point	180°C at 0.039 atm ^a
Log <i>K</i> _{ow}	-0.28 ^b
Water solubility	171 g/L at 25°C ^b
Vapor pressure	0.27 mm Hg at 25°C ^b
Vapor density relative to air	4.2 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

1,3-Propane sultone is used as a chemical intermediate to introduce the sulfopropyl group into molecules and to confer water solubility and an anionic character to the molecules (Dado *et al.* 2006, HSDB 2009). It is used as a chemical intermediate in the production of fungicides, insecticides, cation-exchange resins, dyes, vulcanization accelerators, detergents, lathering agents, bacteriostats, and a variety of other chemicals and as a corrosion inhibitor for mild (untempered) steel (IARC 1999, Dado *et al.* 2006).

Production

1,3-Propane sultone was first produced in the United States in 1963 (IARC 1974). In 1974, the only U.S. producer of 1,3-propane sultone manufactured less than 500 kg (1,100 lb) annually (IARC 1974). No information on the global production of 1,3-propane sultone was available in 1999 (IARC 1999). In 2009, 1,3-propane sultone was produced by one manufacturer each in Europe and China (SRI 2009) and was available from 28 suppliers, including 13 U.S. suppliers (Chem Sources 2009). Reports filed in 1986, 1990, and 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,3-propane sultone totaled 10,000 to 500,000 lb (EPA 2004); no inventory update reports for 1,3-propane sultone were filed in 1994 or 1998.

Exposure

The routes of potential human exposure to 1,3-propane sultone are ingestion, inhalation, and dermal contact. 1,3-Propane sultone is not known to occur naturally. Consumers could potentially be exposed to its residues when using detergents, corrosion inhibitors, and other products manufactured from 1,3-propane sultone. When released to air, 1,3-propane sultone will react with photochemically produced hydroxyl radicals, with a half-life of 8 days, and when released to water or moist soil, it will rapidly hydrolyze (HSDB 2009). 1,3-Propane sultone may occur in the waste streams of industrial facilities making or using it, but is not expected to be present for long periods, because it is readily hydrolyzed (IARC 1974). According to EPA's Toxics Release Inventory, environmental releases of 1,3-propane sultone have not exceeded 750 lb in any year since 1988; in many years, no releases were reported. In 2009, one facility released 260 lb of 1,3-propane sultone, including 250 lb to air and 10 lb to a hazardous-waste landfill (TRI 2009). The potential for occupational exposure is highest for workers involved in the formulation of compounds made from 1,3-propane sultone or the production of its end products (IARC 1974).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of 1,3-propane sultone = U193.

Listed as a hazardous constituent of waste.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = exposure by all routes should be as low as possible.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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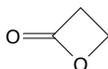
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β-Propiolactone

CAS No. 57-57-8

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)



Carcinogenicity

β-Propiolactone is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

β-Propiolactone caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Oral exposure to β-propiolactone caused cancer of the forestomach (squamous-cell carcinoma) in female rats, and dermal exposure caused benign and malignant skin tumors (papilloma that changed to squamous-cell carcinoma) in mice of unspecified sex. Subcutaneous injection of β-propiolactone caused cancer at the injection site in mice of unspecified sex (fibrosarcoma, adenocarcinoma, and squamous-cell carcinoma) and in rats of both sexes (sarcoma) (IARC 1974). In nursing mice, a single intraperitoneal injection of β-propiolactone caused lymphoma in both sexes and liver tumors (hepatocellular tumors) in males.

Since β-propiolactone was listed in the *Second Annual Report on Carcinogens*, additional studies in experimental animals have been identified. In female mice, oral exposure to β-propiolactone increased the combined incidence of benign and malignant tumors of the forestomach (papilloma and carcinoma) (Hochalter *et al.* 1988, Wattenberg *et al.* 1983, 1987). In male rats, intrarectal administration of β-propiolactone caused benign colon tumors (adenomatous polyps) (Hochalter *et al.* 1988), and inhalation exposure to β-propiolactone caused cancer of the nasal cavity (Sellakumar *et al.* 1987, Snyder *et al.* 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to β-propiolactone.

Properties

β-Propiolactone is a colorless liquid with a pungent, slightly sweet odor at room temperature (Akron 2009). It is soluble in water, miscible with alcohol, acetone, ether, and chloroform, and probably miscible with most polar organic solvents and lipids (HSDB 2009). It is unstable at room temperature, but stable when stored at 5°C in glass containers (Akron 2009). Physical and chemical properties of β-propiolactone are listed in the following table.

Property	Information
Molecular weight	72.1 ^a
Specific gravity	1.146 at 20°C/4°C ^a
Melting point	-33.4°C ^a
Boiling point	61°C at 20 mm Hg ^a
Log <i>K</i> _{ow}	0.462 ^a
Water solubility	370 g/L at 25°C ^a
Vapor pressure	3.4 mm Hg at 25°C ^b
Vapor density relative to air	2.5 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

β-Propiolactone was once a commercially important industrial chemical, and more than 85% of the β-propiolactone produced in the United States was used captively to manufacture acrylic acid and esters (IARC 1974, HSDB 2009). However, β-propiolactone has been replaced in newer manufacturing methods (Bauer 2003). β-Propiolactone has been used to sterilize blood plasma, vaccines, tissue grafts, surgical instruments, and enzymes; as a vapor-phase disinfectant in enclosed spaces; and in organic synthesis (IARC 1974). It has been used as a sporicide against vegetative bacteria, pathogenic fungi, and viruses (HSDB 2009). β-Propiolactone has also been used to inactivate viruses for use in vaccines for animals and humans (Levy *et al.* 1975, Parker 1975, Kurogi *et al.* 1978, Scheidler *et al.* 1998).

Production

β-Propiolactone was first produced commercially in the United States in 1958, and one U.S. company produced β-propiolactone from 1958 until at least 1973 (IARC 1974). U.S. production was approximately 22 million kilograms (48.5 million pounds) in 1972, but less than 454 kg (1,000 lb) in 1975 (HSDB 2009). No data on current production of β-propiolactone were found. In 2009, β-propiolactone was produced by one manufacturer, in Europe (SRI 2009), and was available from twelve suppliers, including seven U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of β-propiolactone were found.

Exposure

Because β-propiolactone is no longer used as a sterilant in medical procedures or in food, the potential for exposure of the general population is limited (HSDB 2009). Potential exposure to waste effluents from production and manufacturing plants is minimal, because of β-propiolactone's short half-life in water (IARC 1974). Occupational exposure may occur by inhalation and dermal contact at industrial facilities where β-propiolactone is used as a chemical intermediate. Occupational exposure may also occur in laboratories where it is used to inactivate viruses for research and vaccine applications. The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 575 workers potentially were exposed to β-propiolactone (NIOSH 1976). No more recent exposure estimates were found.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Exposure Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 500 lb.

Occupational Safety and Health Administration (OSHA)

Potential occupational carcinogen: Engineering controls, work practices, and personal protective equipment are required.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm.

National Institute for Occupational Safety and Health (NIOSH)

β-propiolactone is listed as a potential occupational carcinogen.

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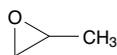
Propylene Oxide

CAS No. 75-56-9

Reasonably anticipated to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as 2-methyloxirane



Carcinogenicity

Propylene oxide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Propylene oxide caused tumors in two rodent species, at several different tissue sites, and by several different routes of exposure. Exposure to propylene oxide by inhalation caused (1) benign and malignant blood-vessel tumors (hemangioma and hemangiosarcoma) in the nasal cavity of mice of both sexes, (2) benign nasal-cavity tumors (pap-

illary adenoma) in rats of both sexes, and (3) benign adrenal-gland tumors (pheochromocytoma) and tumors of the abdominal cavity (mesothelioma) in weanling male rats. Administration of propylene oxide by stomach tube caused forestomach cancer (primarily squamous-cell carcinoma) in female rats, and subcutaneous injection caused cancer at the injection site (fibrosarcoma or pleomorphic sarcoma) in female mice (NTP 1985, IARC 1985, 1987).

Since propylene oxide was listed in the *Sixth Annual Report on Carcinogens*, an additional study in rats has been identified, in which inhalation exposure to propylene oxide caused benign and malignant mammary-gland tumors (fibroadenoma and adenocarcinoma) in females (IARC 1994).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to propylene oxide. In a cohort study of 602 workers potentially exposed to propylene oxide as well as to ethylene oxide, benzene, ethylene chlorohydrin, and other chemicals, no significant associations were found between exposure and cancer at specific tissue sites; however, the results were considered to be inconclusive with respect to propylene oxide (IARC 1985, 1987).

Since propylene oxide was listed in the *Sixth Annual Report on Carcinogens*, additional epidemiological studies have been identified. The International Agency for Research on Cancer (IARC 1994) reviewed several cohort studies of mixed exposures that included propylene oxide, including studies of chemical workers by Gardner *et al.* (1989), Hogstedt *et al.* (1986), and Hogstedt (1988), and one case-control study of specific types of lymphohematopoietic-system cancer that evaluated exposure specifically to propylene oxide (Ott *et al.* 1989). The cohort studies were not informative because they could not distinguish the specific effects of propylene oxide, and IARC concluded that the case-control study was not informative because of limitations in exposure assessment and potential confounding by other risk factors.

Properties

Propylene oxide is an epoxide compound that exists at room temperature as a volatile colorless liquid with an ethereal benzene-like odor (IPCS 1985). It is soluble in water and ethanol and miscible with acetone, benzene, carbon tetrachloride, methanol, and ether. Propylene oxide is very flammable, but it is stable under normal storage conditions (Akron 2009). It is very reactive, particularly with chlorine, ammonia, strong oxidants, and acids. It may polymerize explosively when heated or involved in a fire (IARC 1994, HSDB 2009). Physical and chemical properties of propylene oxide are listed in the following table.

Property	Information
Molecular weight	58.1
Specific gravity	0.8304 at 20/20°C
Melting point	-112.13°C
Boiling point	34.23°C
Log K_{ow}	0.03
Water solubility	590 g/L at 25°C
Vapor pressure	538 mm Hg at 25°C
Vapor density relative to air	2

Source: HSDB 2009.

Use

Propylene oxide is used primarily as a chemical intermediate in the production of other compounds (HSDB 2009). In the United States in 1993, propylene oxide was used to produce the following compounds:

polyurethane polyols (58%), propylene glycols (22%), glycol ethers (5.5%), di- and tri-propylene glycols (3.5%), and miscellaneous compounds (polyalkylene glycols, allyl alcohol, and isopropanolamines) (11%) (CMR 2001). Polyurethane polyols are used to make polyurethane foams, and propylene glycols are used primarily to make unsaturated polyester resins for the textile and construction industries. Propylene oxide is also used in the preparation of lubricants, surfactants, and oil demulsifiers. It is approved for use as a direct and indirect food additive. In addition, propylene oxide has been used as a fumigant for soil and in chambers for the sterilization of packaged foods. It is used as an herbicide, microbicide, insecticide, fungicide, and miticide (HSDB 2009). It is also used as a reactive diluent in preparations for embedding tissues for transmission electron microscopy, in detergent manufacture, and as a component of brake fluids (IARC 1994, HSDB 2009).

Production

Propylene oxide was first prepared in 1860, but commercial production did not begin until the early 1900s (IARC 1985, 1994). Between 1977 and 1993, annual production of propylene oxide ranged from 1.7 billion pounds to 2.73 billion pounds. During the 1990s, production increased about 4% per year, and growth was expected to be about 3% over the next decade. In 1995, propylene oxide was the 35th-highest-volume chemical produced in the United States. Production was 3.2 billion pounds in 1998, 3.62 billion pounds in 1999, 3.69 billion pounds in 2000, and 3.5 billion pounds in 2002. The total production capacity for the five U.S. propylene oxide manufacturing facilities operating in 2001 was 4.98 billion pounds. The projected demand for 2004 was 4.07 billion pounds (CMR 2001, HSDB 2009). In 2009, propylene oxide was produced by 47 manufacturers worldwide, including 5 in the United States (SRI 2009), and was available from 49 suppliers, including 17 U.S. suppliers (ChemSources 2009). Reports filed under the Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that between 1988 and 2006, production plus imports of propylene oxide totaled over 1 billion pounds (EPA 2004, 2009). U.S. imports of propylene oxide decreased from between 25 million and 50 million pounds in the 1970s and 1980s to 36,000 kg (79,000 lb) in 1997. Imports were 13.1 million kilograms (29 million pounds) in 2004 and 1.1 million kilograms (2.4 million pounds) in 2008. Compared with domestic production, imports have been negligible in recent years. U.S. exports of propylene oxide increased from between 99 million and 166 million pounds in the 1970s and early 1980s to 238 million kilograms (526 million pounds) in 2006, falling to 179 million kilograms (395 million pounds) in 2008 (HSDB 2009, USITC 2009).

Exposure

The routes of exposure to propylene oxide are inhalation, ingestion, and incidental dermal exposure. Consumers may be exposed through ingestion of propylene oxide residues in foods resulting from its use as an indirect food additive or by contact with consumer products containing propylene oxide. EPA has established tolerance limits for propylene oxide based on residues from fumigation of cocoa beans, nutmeats, herbs and spices, and some fruits (e.g., figs, prunes, and raisins) (EPA 2006). Consumer products with the highest concentrations of propylene oxide include automotive and paint products. One automotive product lists propylene oxide as an ingredient at a concentration of 0.1% to 0.5% (HPD 2009).

According to EPA's Toxics Release Inventory, environmental releases of propylene oxide declined from a high of 4.9 million pounds in 1988 to a low of 374,000 lb in 2001. In 2007, 97 facilities produced,

processed, or otherwise used propylene oxide, and 84 facilities released a total of 436,321 lb; 97% of releases were to air (TRI 2009).

The primary route of occupational exposure to propylene oxide is inhalation, during its use in the production of polyurethane polyols and propylene glycol or as a fumigant (IARC 1994, HSDB 2009). For almond and walnut fumigation, the daily time-weighted-average exposure concentration was 0.71 ppm (geometric mean) for combined non-specific exposure and exposure during chamber unloading (adjusted for exposure duration) (EPA 2006). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 268,433 workers potentially were exposed to propylene oxide (NIOSH 1976), and the National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that about 420,000 workers, including 317,000 women, potentially were exposed (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of propylene oxide on ships and barges, and requirements for Notices of Arrival and Notice of Hazardous Conditions have been established.

Department of Transportation (DOT)

Propylene oxide is considered a hazardous material and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of propylene oxide is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Reportable quantity (RQ) = 100 lb.

Threshold planning quantity (TPQ) = 10,000 lb.

Toxics Release Inventory: Listed substance subject to reporting requirements.

Federal Insecticide, Fungicide, and Rodenticide Act

Tolerances for residues of propylene oxide when used as a postharvest fumigant: = 300 ppm for dried garlic, dried herbs and spices, tree nuts, dried onion; = 200 ppm for cacao bean and cocoa powder; = 3 ppm for fig; = 2 ppm for plum, prune; = 1 ppm for grape, raisin.

Food and Drug Administration (FDA)

Limitations on propylene oxide use in food additives permitted for direct addition to food for human consumption and in food contact materials are prescribed in 21 CFR 172, 173, 175, 176, and 178.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 100 ppm (240 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 400 ppm.

Listed as a potential occupational carcinogen.

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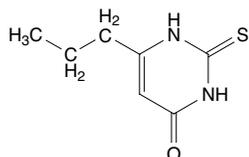
Propylthiouracil

CAS No. 51-52-5

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as 6-*n*-propylthiouracil or PROP



Carcinogenicity

Propylthiouracil is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to propylthiouracil caused benign or malignant thyroid tumors (follicular-cell adenoma or carcinoma) in four species of rodents: mice (of unspecified sex), rats and hamsters of both sexes, and male guinea pigs. Some metastases were observed in hamsters. Pro-

pylthiouracil also caused benign tumors of the anterior pituitary gland (chromophobe adenoma) in mice. It was administered to mice in the diet and to the other rodents in drinking water (IARC 1974, 1982).

Since propylthiouracil was listed in the *Fourth Annual Report on Carcinogens*, an additional study in rats has been published, which reported that propylthiouracil administered in drinking water also caused parathyroid tumors (Walker *et al.* 1994).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to propylthiouracil. There has been one case report of acute myeloblastic leukemia in a woman following propylthiouracil treatment (Aksoy *et al.* 1974).

Properties

Propylthiouracil is a thioamide compound that exists as a white crystalline powder at room temperature. It is slightly soluble in water, sparingly soluble in acetone and ethyl alcohol, and practically insoluble in ether, chloroform, and benzene. It is stable under normal temperatures and pressures (Akron 2009). It forms complexes with metals and reacts with sulfhydryl-oxidizing agents (IARC 1974, HSDB 2009). Physical and chemical properties of propylthiouracil are listed in the following table.

Property	Information
Molecular weight	170.2 ^a
Melting point	219°C to 221°C ^a
Log <i>K</i> _{ow}	0.98 ^a
Water solubility	1.2 g/L at 25°C ^a
Vapor pressure	6.92 × 10 ⁻⁸ mm Hg at 25°C ^b
Dissociation constant (p <i>K</i> _a)	7.63 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Propylthiouracil has been used since the 1940s as an antithyroid agent for the treatment of hyperthyroidism (IARC 1974, 2001, Farwell and Braverman 2001). It may also be given to patients with alcoholic liver disease and has been shown to decrease mortality by half in these patients in a two-year double-blind study (Orrego *et al.* 1987). Propylthiouracil is also used to test taste perception for bitterness (Ly and Drewnowski 2001); in this context, it is referred to as 6-*n*-propylthiouracil (PROP). The ability to taste PROP is genetically determined and affects an individual's food choices in daily life. Propylthiouracil was formerly used as a metabolic depressant to promote fattening of cattle (IARC 1974, 2001).

Production

In 2009, propylthiouracil was produced by two manufacturers in Europe, two in China, and none in the United States (SRI 2010) and was available from 25 suppliers, including 10 U.S. suppliers. No data on U.S. imports or exports of propylthiouracil were found.

Exposure

The primary route of potential human exposure to propylthiouracil is ingestion as a drug. Three pharmaceutical products approved by the U.S. Food and Drug Administration contain 50 mg of propylthiouracil as the active ingredient (FDA 2009). The initial dose in adults is usually 300 mg per day in three equal doses, and the maintenance dose is 100 to 150 mg per day. In children, the initial dose is 5 to 7 mg/kg of body weight per day administered in three equal doses, and the maintenance dose is one third to two thirds of the initial dose (Drugs.com 2010). Occupational exposure may occur during the production, for-

mulation, packaging, or administration of pharmaceutical products containing propylthiouracil. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 3,331 workers, including 1,666 women, mostly in the Health Services industry, potentially were exposed to propylthiouracil (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Propylthiouracil is a prescription drug subject to specific labeling requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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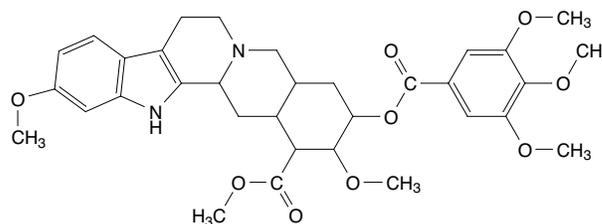
Reserpine

CAS No. 50-55-5

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as methyl 18 β -hydroxy-11,17 α -dimethoxy-3 β ,20 α -yohimban-16 β -carboxylate 3,4,5-trimethoxybenzoate (ester)



Carcinogenicity

Reserpine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to reserpine caused tumors in two rodent species and at several different tissue sites. Dietary administration of reserpine caused cancer of the mammary gland in female mice, cancer of the genitourinary tract (undifferentiated carcinoma of the seminal vesicles) in male mice, and benign tumors of the adrenal gland (pheochromocytoma) in male rats (Griesemer and Dunkel 1980, IARC 1980, NTP 1982). Since reserpine was listed in the *Second Annual Report on Carcinogens*, additional studies in rodents have been identified. Reserpine administered by subcutaneous injection also caused mammary-gland tumors in mice and adrenal-gland tumors (pheochromocytoma) in rats (IARC 1987).

Cancer Studies in Humans

Several case-control epidemiological studies examined the relationship between breast cancer and the use of reserpine (or *Rauwolfia* derivatives; see Properties); most of these studies reported statistically nonsignificant risk estimates of between 1 and 2. These studies do not provide conclusive evidence of a causal association between reserpine use and cancer (IARC 1976).

Since reserpine was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. Case-control and cohort studies on the relationship between breast cancer and exposure to reserpine reviewed by the International Agency for Research on Cancer reported inconsistent results (IARC 1982, 1987). However, one large study reported a significantly increased risk of breast cancer among individuals who had used reserpine for over 10 years (Stanford *et al.* 1986). A review and pooled analysis of all published case-control studies found a small but significant increase in the risk of breast cancer with reserpine use; however, this finding was not confirmed by prospective studies (Grossman *et al.* 2002).

Properties

Reserpine a biologically active naturally occurring alkaloid (NTP 1982) that exists at room temperature as a white or pale-buff to yellow odorless powder. It is practically insoluble in water; freely soluble in chloroform, methylene chloride, and glacial acetic acid; soluble in benzene and ethyl acetate; and slightly soluble in methanol, ethanol, acetone, ether, and weak solutions of acetic and citric acids. It

is stable under normal storage conditions but is subject to oxidation and hydrolysis (Akron 2009). Reserpine acquires a yellow color with pronounced fluorescence, especially after the addition of acid or exposure to light. When heated to decomposition, it emits toxic fumes of nitrogen oxides (IARC 1976, HSDB 2009). Physical and chemical properties of reserpine are listed in the following table.

Property	Information
Molecular weight	608.7 ^a
Melting point	264.5°C ^a
Log K_{ow}	3.32 ^b
Water solubility	0.073 g/L at 30°C ^a
Vapor pressure	4.51×10^{-16} mm Hg at 25°C ^b
Dissociation constant (pK_a)	6.6 ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Reserpine is produced by several members of the genus *Rauwolfia*, a climbing shrub indigenous to southern and southeast Asia. It is used to lower blood pressure and reduce the heart rate and as a tranquilizer and sedative in humans. It has also been used as a radioprotective agent and experimentally as a contraceptive (Nakayama and Nakamura 1978, Chan and Tang 1984). Extracts of *Rauwolfia serpentina* have been used medicinally in India for centuries. They were used in traditional Hindu medicine for a variety of conditions, including snakebite, hypertension, insomnia, and insanity. Reserpine has also been used as a tranquilizer and sedative in animal feeds (IARC 1976).

Production

Reserpine is extracted from the roots of *Rauwolfia serpentina* with alcohol or aqueous acid and then purified. In 1976, the volume of reserpine sold in the United States for medical use was approximately 440,000 lb. In 1974, there were six U.S. producers of reserpine (IARC 1976). In 2009, reserpine was produced by seven manufacturers, all in India (SRI 2009); it was available from 12 U.S. suppliers (ChemSources 2009), and four drug products approved by the U.S. Food and Drug Administration containing reserpine as an active ingredient were manufactured by two pharmaceutical firms (FDA 2009). In addition, over 100 discontinued drug products from over 40 pharmaceutical firms were identified as containing reserpine as an active ingredient. U.S. imports of reserpine totaled 22 lb in 1970 and 103 lb in 1983 and 1984, while U.S. exports of reserpine were negligible (HSDB 2009). No more recent information on U.S. imports or exports of reserpine was found.

Exposure

Patients receiving therapy for hypertension may be exposed to reserpine, which is administered orally. Numerous advertisements for the sale of *Rauwolfia serpentina* and extracts from the plant as herbal products or for homeopathic medicine were identified on the Internet in 2010. The use of reserpine as a drug may result in its release to the environment in various waste streams. Occupational exposure may occur through inhalation or dermal contact at workplaces where reserpine is produced or used (HSDB 2009). Health professionals such as doctors, nurses, and pharmacists may be exposed while dispensing, preparing, or administering the drug. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 5,611 workers, including 2,414 women, potentially were exposed to reserpine (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Any orally administered prescription drug for human use requires child-resistant packaging.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 5,000 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of reserpine = U200.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Reserpine is a prescription drug subject to labeling and other requirements.

All oral dosage drug products containing more than 1 mg of reserpine have been withdrawn from the market and may not be compounded, because such drug products were found to be unsafe or not effective.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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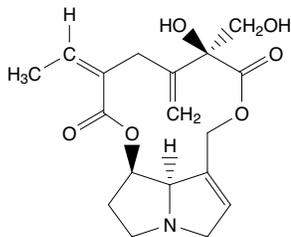
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Riddelliine

CAS No. 23246-96-0

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)



Carcinogenicity

Riddelliine is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting data from studies on mechanisms of carcinogenesis.

Cancer Studies in Experimental Animals

Oral exposure to riddelliine caused tumors at several different tissue sites in mice and rats and early onset of tumors in rats. Administration of riddelliine by stomach tube throughout the course of two-year studies caused blood-vessel cancer (hemangiosarcoma) of the liver in male mice and in rats of both sexes. It also caused benign liver tumors (hepatocellular adenoma) and mononuclear-cell leukemia in rats of both sexes and increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in female mice. Benign liver tumors (hepatocellular adenoma) were observed in some female rats in a 13-week study (Chan *et al.* 2003, NTP 2003).

Studies on Mechanisms of Carcinogenesis

Riddelliine and other pyrrolizidine alkaloids are absorbed primarily via ingestion (although dermal absorption can occur), distributed to the liver, and excreted in the urine and feces. Riddelliine is metabolized in the liver to two reactive metabolites, *R*- and *S*-dihydropyrrolizine (DHP) (also known as dehydroretronecine and dehydroheliotridine or (\pm)-6,7-dihydro-7-hydroxy-1-hydroxymethyl-5*H*-pyrrolizine), by the cytochrome P450 isozymes CYP3A and CYP2B6. Both *R*- and *S*-DHP have been shown to cause tumors in rodents (NTP 2008).

DHP can bind DNA, which may be a key step leading to its genotoxicity and tumorigenicity. A set of eight DHP-derived adduct peaks was detected in DNA reacted with riddelliine in the presence of rat or human microsomes (Xia *et al.* 2003, NTP 2008). Dose-dependent DHP adduct formation also was detected in livers of rats exposed to riddelliine (Yang *et al.* 2001, NTP 2008). Adduct levels were higher in DNA in endothelial cells than in parenchymal cells in rats and were more persistent in endothelial cells than in parenchymal cells in both rats and mice, suggesting that tumor specificity was due to higher levels of DNA damage in the endothelial cells, from which liver hemangiosarcomas are formed (Chou *et al.* 2004, NTP 2008). The kinetic parameters for formation of DHP are comparable in human and rat microsomes, and the same profile of DHP-adduct peaks was detected in humans and rats (Xia *et al.* 2003). In addition, other pyrrolizidine alkaloids have been shown to be metabolized to DHP, and it has been proposed that any pyrrolizidine alkaloid that is metabolized to DHP will be carcinogenic in rodents (Fu *et al.* 2002). Studies in rats have shown that pyrrolizidine alkaloids cause liver tumors

and, to a lesser extent, tumors at other tissue sites, including the central nervous system, lung, pancreas, urinary bladder, skin, testes, pituitary gland, and adrenal gland (NTP 2008). It has been proposed that tumor specificity and relative species susceptibility to riddelliine carcinogenicity may be due to variability in the balance between the formation of toxic metabolites, such as DHP, and the availability of glutathione or other detoxification pathways (Fu *et al.* 2002b).

The evidence is sufficient to conclude that the metabolites of riddelliine are genotoxic, both *in vitro* and *in vivo*, and the data suggest that genotoxicity contributes to riddelliine's carcinogenic activity. In the *cH* gene mutation assay in transgenic Big Blue rats, riddelliine increased the frequency of mutations in nonneoplastic endothelial cells (but not in parenchymal cells). The predominant mutations were G:C to T:A transversions, which is consistent with riddelliine-induced formation of DNA adducts involving G:C base pairs (Mei *et al.* 2004a,b). These changes were consistent with mutations in the *K-ras* oncogene identified in riddelliine-induced hemangiosarcomas from mice (Hong *et al.* 2003). The DHP metabolites clearly form several different DNA adducts in cultured cells as well as in exposed animals (NTP 2008). Riddelliine also caused base-pair substitutions in *Salmonella typhimurium*. In mammalian cells *in vitro*, it caused sister chromatid exchange and chromosomal aberrations in Chinese hamster ovary cells, cell transformation in BALB/c-3T3 fibroblast cells, and DNA cross-linking (but not DNA strand breaks) in bovine kidney epithelial cells. In rats exposed *in vivo*, riddelliine induced S-phase synthesis in hepatocytes and endothelial cells and increased p53 protein production in endothelial cells but did not induce micronucleus formation in polychromatic erythrocytes. In mice, riddelliine caused unscheduled hepatocyte DNA synthesis (in females only), but did not induce micronucleus formation (NTP 2008).

Riddelliine metabolites appear to cause damage and local inflammation (arteritis) in endothelial cells, as evidenced by abnormally large cell nuclei and enlarged cells, resulting in complete or partial occlusion of the vessel lumina and accumulation of intravascular macrophages in many organs (NTP 2008). Reactive oxygen species produced by macrophages and other mediators of the inflammatory response may have a role in the carcinogenicity of riddelliine through the depletion of cellular detoxification pathways. However, a specific biochemical pathway linking inflammation to riddelliine carcinogenicity has not been determined. A mechanism for the pathogenesis of hemangiosarcomas in the liver of animals exposed to riddelliine has been proposed by Nyska *et al.* (2002) and Moyer *et al.* (2004). Short-term exposure to riddelliine in rats increased apoptosis and S-phase nuclei in endothelial cells and hepatocytes, and increased levels of p53 protein were detected in endothelial cells. The nuclear and cytoplasmic enlargement of endothelial cells causes sinusoidal obstruction and local hypoxia, which stimulates the production of vascular endothelial growth factor, an endothelial cell-specific mitogen, by hepatocytes. Development of hemangiosarcoma in the liver may result from endothelial-cell DNA-adduct formation, apoptosis, proliferation of endothelial cells, and mutations (Nyska *et al.* 2002, Moyer *et al.* 2004).

Riddelliine also exhibits significant non-cancer toxicity and pathology. It is acutely and chronically toxic in animals, and human toxicity has been demonstrated for consumption of foods or herbal products containing riddelliine or other pyrrolizidine alkaloids. The primary toxic effect of riddelliine, venous occlusion, occurs in the same target tissue (i.e., liver) as the primary tumor, and the non-cancer effects are likely to involve the same reactive intermediate(s). However, given the strong evidence for a genotoxic mode of action, there is no reason to suspect that tumorigenicity is due solely to compensatory cell proliferation (NTP 2008).

Cancer Studies in Humans

No studies on the relationship between human cancer and exposure specifically to riddelliine were identified.

Properties

Riddelliine is a pyrrolizidine alkaloid of the macrocyclic diester class and exists in plants as the free-base alkaloid and as an *N*-oxide, which can be converted back to riddelliine after ingestion. Both riddelliine and riddelliine *N*-oxide are white crystalline solids. In water, riddelliine is sparingly soluble, and riddelliine *N*-oxide is soluble. Alcohol and aqueous solutions of riddelliine are stable at room temperature when protected from light; the solid form is stable at room temperature in diffuse light for several years. Riddelliine reacts readily with oxidizing agents to form DHP and other derivatives; however, it reacts slowly with atmospheric oxygen. It hydrolyzes readily in aqueous alkalis. Riddelliine *N*-oxide in solid form is stable at freezer temperature but not at room temperature (IARC 1976, NTP 2008). Physical and chemical properties of riddelliine and riddelliine *N*-oxide are listed in the following table.

Property	Riddelliine	Riddelliine <i>N</i> -oxide
Molecular weight	349.4	365.4
Melting point (decomposes)	197°C to 198°C	156°C to 158°C
Hydrochloride	225°C to 226°C	N/A
Methodide	260°C to 262°C	N/A

Source: NTP 2008. N/A = not applicable.

Use

Riddelliine-containing plants are not used for food in the United States, and riddelliine and riddelliine *N*-oxide have no known commercial uses. However, the riddelliine-containing plant *Senecio longilobus* has been used in medicinal herb preparations in the United States, and *S. jacobaea* and *S. vulgaris*, both of which have been shown to contain riddelliine, are used in medicinal preparations in other parts of the world (Mattocks 1986).

Production and Occurrence

The only known production of riddelliine has been for experimental purposes by purification from *S. riddellii*. Riddelliine *N*-oxide has been synthesized from riddelliine by oxidation with hydrogen peroxide in ethanol (Molyneux *et al.* 1991). No vendors for these products were identified. However, riddelliine occurs naturally in plants (primarily of the genus *Senecio*) found in the western United States and other parts of the world. At least 13 *Senecio* species worldwide have been identified that are used in herbal medicines or possibly as food. The following plant species have been identified as containing riddelliine (Mattocks 1986, Hartmann and Witte 1995, NTP 2008) (*indicates North American species):

- *Senecio aegypticus*
- *Senecio ambrosioides* (*S. brasiliensis*)
- *Senecio cruentus*
- *Senecio cymbalarioides*
- *Senecio desfontanei* (*S. coronopifolius*)
- *Senecio douglasii* var. *longilobus** (*S. longilobus*) (woody or threadleaf groundsel)
- *Senecio eremophilus*
- *Senecio jacobaea** (erucifoline chemotype) (tansy ragwort, stinking willie)
- *Senecio riddellii** (Riddell's ragwort, Riddell's groundsel)
- *Senecio spartioides** (broom groundsel)
- *Senecio vulgaris** (common groundsel)
- *Senecio pseudo-orientalis*

- *Senecio vernalis*
- *Crotalaria juncea*

The prototypical riddelliine-containing *Senecio*, Riddell's groundsel (*S. riddellii*), generally grows in desert areas of western North America, especially in sandy soils. It is a low, shrubby plant with bright-green, thread-like leaves and intensely yellow composite flowers. The plant sprouts in the early spring and dies back to a woody crown in the early fall, although sufficient moisture from summer rains may initiate regrowth on the stems. The early-season growth and regrowth at periods when little other green leafy material is available may make it attractive to grazing animals. This plant was one of the earliest *Senecio* species to be identified as poisonous to animals, causing "walking disease" in horses in Nebraska and adjacent areas of Colorado and Wyoming. The syndrome is characterized by aimless wandering and cirrhosis of the liver (Johnson *et al.* 1985b).

Riddelliine and riddelliine *N*-oxide are the predominant alkaloids in *S. riddellii*, occurring in yields of up to 18% of the dry weight of the plant (Molyneux and Johnson 1984); however, alkaloid content may be highly variable, depending on growth stage, environmental conditions, and location (Johnson *et al.* 1985a). It has been calculated that at 18% total pyrrolizidine alkaloid, as little as 33 g of dry or 176 g of fresh *S. riddellii* consumed per day would be toxic to a 300-kg cow. The environmental fate of riddelliine and other pyrrolizidine alkaloids is not well established. In *Senecio* species, the alkaloids are biosynthesized in the roots and, as the *N*-oxides, translocated in the phloem to the flower structure, where they are preferentially stored (Hartmann *et al.* 1989). After flowering, the pyrrolizidine alkaloid content of the remaining plant is drastically reduced, presumably because the majority of the alkaloid is dispersed in seeds and flower fragments. Nevertheless, the alkaloid content in the remaining leaves can be appreciable. For example, in *S. riddellii* collected in Oklahoma over a five-year period, the total alkaloid content in the leaves immediately before senescence ranged from 3% to 6% on a dry-weight basis (Johnson *et al.* 1985a).

No data on U.S. production volume, sales, or imports of riddelliine or riddelliine-containing plants were found.

Exposure

Herbal products containing pyrrolizidine alkaloids, some from plants of the genus *Senecio*, have been extensively documented as causing toxicity in humans (Huxtable 1989). Two cases of accidental poisoning of infants were reported from the southwestern United States, in which *S. longilobus*, a species known to contain riddelliine, as well as the alkaloids seneciphylline, senecionine, and retrorsine, was accidentally used to prepare an herbal tea known as *gordolobo yerba* (Stillman *et al.* 1977). The distribution of *S. longilobus* was traced to a major U.S. importer, who also was a major supplier of herbs in the western United States (Huxtable 1980). *Senecio*-containing products have been inadvertently distributed by pharmacies and herb stores and also could be consumed by people who gather herbs for private use (Fox *et al.* 1978).

Although *Senecio* species containing riddelliine are not used as food plants in the United States, human exposure could result from direct contamination of foodstuffs by parts of *Senecio* plants or from indirect introduction of the alkaloid through products derived from animals that have fed on the plants. There is thus the potential for cumulative effects from low-level exposures. Evidence for ingestion of contaminated products comes from reports of toxicity in animals and humans. Outside of the United States, accidental human poisoning from grains and flour contaminated with *Senecio* plant parts has been reported. Studies of cows fed *Senecio* plants demonstrated that pyrrolizidine alkaloids could be transmitted in milk, with rid-

delliine *N*-oxide concentrations estimated as high as 5 mg/L (Molyneux and James 1990). Pyrrolizidine alkaloids other than riddelliine have been detected in eggs, and honey has been shown to contain either pyrrolizidine alkaloids or pollen from pyrrolizidine alkaloid-containing plants (NTP 2008).

Regulations

No regulations or guidelines relevant to reduction of exposure to riddelliine were identified.

Warnings and Alerts

Food and Drug Administration (FDA)

In a 2001 alert (FDA 2001), the agency strongly recommended that firms marketing a product containing comfrey or another source of pyrrolizidine alkaloids remove the product from the market and alert its customers to immediately stop using the product. The agency advised that it was prepared to use its authority and resources to remove products from the market that appeared to violate the Federal Food, Drug, and Cosmetic Act.

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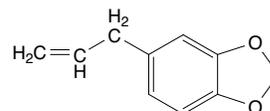
Safrole

CAS No. 94-59-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as 5-(2-propenyl)-1,3-benzodioxole



Carcinogenicity

Safrole is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Safrole caused liver tumors in two rodent species and by two different routes of exposure. Dietary administration of safrole caused liver cancer (hepatocellular carcinoma) in male mice and benign or malignant liver tumors (hepatocellular carcinoma or adenoma or cholangiocarcinoma) in rats of both sexes (IARC 1972, 1976). Liver cancer (hepatocellular carcinoma) was also observed in mice of both sexes administered safrole by stomach tube from 7 to 28 days of age, followed by dietary exposure for up to 82 weeks, and in infant male mice administered safrole by subcutaneous injection.

Since safrole was listed in the *Second Annual Report on Carcinogens*, an additional study in mice has been identified. The incidence of liver tumors (adenoma and carcinoma) was increased in male mice exposed during infancy via milk and in adult female mice administered safrole in the diet (Vesselinovitch 1983).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to safrole.

Properties

Safrole, a naturally occurring substance, is a derivative of the aromatic phenol ether 1,3-benzodioxole (HSDB 2009). It exists at room temperature as a colorless or pale-yellow oil with an odor of saffras. It is practically insoluble in water, insoluble in glycerine, slightly soluble in propylene glycol, soluble in alcohol, and miscible with chloroform and ether. Physical and chemical properties of safrole are listed in the following table.

Property	Information
Molecular weight	162.2 ^a
Density	1.1 g/cm ³ at 20°C ^a
Melting point	11.2°C ^a
Boiling point	234.5°C ^a
Log <i>K</i> _{ow}	3.45 ^b
Water solubility	0.121 g/L at 25°C ^b
Vapor pressure	0.0618 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Safrole has been used as a flavoring agent in drugs and in the manufacture of heliotropin, perfumes, soaps, and piperonyl butoxide (a compound used in a variety of insecticides to enhance the pesticidal properties of other active ingredients) (IARC 1972, 1976, HSDB 2009). Safrole has also been used as a preservative in mucilage and library paste and as a flotation frother. Oil of sassafras, which contains safrole, was formerly used to flavor some soft drinks, such as root beer. However, this use or any other addition of safrole or oil of sassafras to food was banned in the United States in 1960 (IARC 1972, 1976, HSDB 2009). Safrole has also been used in the illicit production of the drug 3,4-methylenedioxyamphetamine (MDMA, or ecstasy), and the U.S. Drug Enforcement Administration has designated safrole a List I Chemical (DEA 2004, 2009).

Production

Safrole is produced by distillation of oils rich in safrole (IARC 1976). U.S. production of safrole was 257,000 lb in 1969 and 277,000 lb in 1970, but had fallen to 12,000 lb by 1977 (IARC 1976, HSDB 2009). In 2009, safrole was manufactured by only one facility worldwide, in the United States (SRI 2009), and was available from 11 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of safrole totaled 10,000 to 500,000 lb in 1998 (EPA 2004) and less than 500,000 lb in 2006 (EPA 2009); no other inventory update reports for safrole were filed. U.S. imports of safrole were 36,000 lb in 1980 (HSDB 2009) and ranged from 11,000 to 132,000 lb in 1997, 2003, 2004, and 2005 (USITC 2009). U.S. exports of safrole were 6,600 lb in 1996 and 35,200 lb in 1998.

Exposure

The potential routes of exposure to safrole are inhalation, ingestion, and dermal contact (HSDB 2009). Safrole may be ingested in edible spices, including sassafras, cinnamon, nutmeg, mace, star anise, ginger, black and white pepper, and from chewing betel quid; all of these substances contain naturally occurring safrole at low levels (IARC 1976, Archer and Jones 2002, HSDB 2009). Safrole is also present in herbal products derived from the sassafras tree, including the creole herb gumbo filé (Carlson and Thompson 1997). The concentration of safrole can be reduced during the cooking process (Farag and Abo-Zeid 1997). Based on common ingestion patterns, the estimated daily intake of safrole is 0.3 mg (Rietjens *et al.* 2005). Safrole was also identified as a minor constituent of bidi cigarettes (mean concentration = 33 µg per cigarette) (Stanfill *et al.* 2006) and regular tobacco cigarettes (median concentration = 5.2 ng/g of tobacco) (Stanfill and Ashley 1999). Safrole may also be a contaminant of MDMA, of which safrole is a major ingredient (Swist *et al.* 2005).

According to EPA's Toxics Release Inventory, relatively small amounts of safrole have been released to the environment since 1988, mostly as air emissions, except in 1999 and 2001, when a large amount of safrole was released to on-site hazardous-waste landfills or off-site non-hazardous-waste landfills. In 2007, two facilities released a total of 1,000 lb of safrole, each facility releasing roughly half the total (TRI 2009); one facility released the waste to air, and the other to an off-site landfill.

Occupational exposure to safrole may occur by inhalation or dermal contact (HSDB 2009). Health professionals, such as pharmacists, physicians, and nurses, could be exposed during formulation, preparation, administration, or clean-up of drugs containing safrole or sassafras. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 6,475 workers, including 5,761 women, potentially were exposed to safrole (NIOSH 1990).

Regulations

Drug Enforcement Agency (DEA)

Safrole is listed as a Class I chemical, and manufacturers, distributors, importers and exporters are subject to record-keeping, reporting, and other requirements, as prescribed in 21 CFR 1309, 1310, and 1313.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of safrole = U203.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Safrole is prohibited from direct addition to food or use as human food.

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Selenium Sulfide

CAS No. 7446-34-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Selenium sulfide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to selenium sulfide caused tumors in two rodent species and at two different tissue sites. Administration of selenium sulfide by stomach tube caused liver cancer (hepatocellular carcinoma) in rats of both sexes and in female mice. In female mice, it also increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) (NCI 1980b). When applied topically, selenium sulfide and Selsun, an antidandruff shampoo containing 2.5% selenium sulfide, did not cause tumors in mice; however, these studies were considered inconclusive, because the study length was limited to 88 weeks by the animals' early deaths resulting from amyloidosis (NCI 1980a,c).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to selenium sulfide.

Properties

Selenium sulfide is a selenium salt that exists as a yellow-orange to bright-orange tablet or powder at room temperature. It is insoluble in water or ether and soluble in carbon disulfide. Selenium sulfide has a molecular weight of 111.0 and a specific gravity of 3.056 at 0°C (HSDB 2009).

Use

Selenium sulfide is used as an active ingredient in anti-dandruff shampoos and as a constituent of fungicides (ATSDR 2003).

Production

No data were found on selenium sulfide production volume. In the early 1970s, about 440 lb of selenium sulfide was consumed for pharmaceutical and cosmetic products (NCI 1980b). In 2009, selenium sulfide was produced by seven manufacturers worldwide, including one in the United States (SRI 2010), and was available from 17 suppliers, including 10 U.S. suppliers (ChemSources 2009). Four products containing selenium sulfide as an active ingredient are approved by the U.S. Food and Drug Administration (FDA 2009). No recent data on U.S. imports or exports of selenium sulfide were found.

Exposure

The routes of potential human exposure to selenium sulfide are dermal contact, inhalation, and occasional accidental ingestion. Prescription and nonprescription shampoos or lotions for treatment of dandruff or seborrheic dermatitis contain 2.5% and 1% selenium sulfide, respectively. Shampoos containing 1% selenium sulfide are recommended for use at least twice a week. Shampoos containing 2.5% selenium sulfide are recommended for use twice a week for the first two weeks and once a week or less thereafter. The 2.5% lotion may

be used once a day for seven days to treat tinea versicolor (a fungal infection of the of skin) (MedlinePlus 2008). Although residues of selenium sulfide may remain on the scalp after rinsing, there is no substantial absorption through intact skin. Absorption has been reported in patients with open lesions on the scalp or in patients using a 1% cream on the back (NCI 1980c). A patient with scalp lesions who used selenium shampoos had levels of selenium sulfide as high as 32 µg/mL in her urine (NCI 1980b).

No data on the environmental occurrence of selenium sulfide were located. Selenium is a naturally occurring element that is widely distributed throughout the environment, occurring in groundwater, surface water, rocks, soil, and food (ATSDR 2003).

Workers potentially are exposed to airborne selenium sulfide dust during production, formulation, and packaging of consumer products. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 2,965 workers, including 2,491 women, potentially were exposed to selenium sulfide (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Selenium compounds are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Selenium compounds are listed as hazardous air pollutants.

Clean Water Act

Biosolids Rule: Limits have been established for selenium in biosolids (sewage sludge) when used or disposed of via land application.

Effluent Guidelines: Selenium compounds are listed as toxic pollutants.

Water Quality Criteria: Based on fish or shellfish and water consumption = 170 µg/L for selenium; based on fish or shellfish consumption only = 4,200 µg/L for selenium.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Selenium compounds are listed substances subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of selenium sulfide = U205.

Selenium compounds are listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.05 mg/L for selenium.

Food and Drug Administration (FDA)

Selenium sulfide is permitted in antidandruff shampoos and for the control of seborrheic dermatitis at concentrations not to exceed 1% for selenium sulfide or 0.6% for micronized selenium sulfide.

Maximum permissible level in bottled water = 0.05 mg/L for selenium.

Selenium is regulated as a prescription drug subject to labeling and other requirements.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 0.2 mg/m³ (as Se) for selenium compounds except selenium hexafluoride.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m³ for selenium and compounds.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 1 mg/m³ (as Se).

Recommended exposure limit (REL) = 0.2 mg/m³ (as Se) for selenium compounds, except selenium hexafluoride.

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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Silica, Crystalline (Respirable Size)

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Sixth Annual Report on Carcinogens* (1991)

Also known as crystalline silicon dioxide

Carcinogenicity

Respirable crystalline silica, primarily quartz dusts occurring in industrial and occupational settings, is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. Respirable crystalline silica was first listed in the *Sixth Annual Report on Carcinogens* in 1991 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals; the listing was revised to *known to be a human carcinogen* in the *Ninth Report on Carcinogens* in 2000.

Cancer Studies in Humans

Exposure of workers to respirable crystalline silica is associated with elevated rates of lung cancer. The link between human lung cancer and exposure to respirable crystalline silica was strongest in studies of quarry and granite workers and workers involved in ceramic, pottery, refractory brick, and diatomaceous earth industries. Human cancer risks are associated with exposure to respirable quartz and cristobalite but not to amorphous silica. The overall relative risk is approximately 1.3 to 1.5, with higher risks found in groups with greater exposure or longer time since first exposure. Silicosis, a marker for exposure to silica dust, is associated with elevated lung cancer rates, with relative risks of 2.0 to 4.0. Elevated risks have been seen in studies that accounted for smoking or asbestos exposure, and confounding by co-exposure is unlikely to explain these results (IARC 1997).

Cancer Studies in Experimental Animals

In rats, exposure to various forms of respirable crystalline silica by inhalation or intratracheal instillation consistently caused lung cancer (adenocarcinoma or squamous-cell carcinoma). Single intrapleural or intraperitoneal injections of various forms of respirable crystalline silica also caused lymphoma in rats (IARC 1997).

Studies on Mechanisms of Carcinogenesis

Respirable crystalline silica deposited in the lungs causes epithelial injury and macrophage activation, leading to inflammatory responses and proliferation of the epithelial and interstitial cells. In humans, respirable crystalline silica persists in the lungs, culminating in the development of chronic silicosis, emphysema, obstructive airway disease, and lymph-node fibrosis. Respirable crystalline silica stimulates (1) release of cytokines and growth factors from macrophages and epithelial cells, (2) release of reactive oxygen and nitrogen intermediates, and (3) oxidative stress in the lungs. All of these pathways contribute to lung disease. Marked and persistent inflammation, specifically inflammatory-cell-derived oxidants, may provide a mechanism by which respirable crystalline silica exposure can result in genetic damage in the lung parenchyma. In one study, human subjects exposed to respirable crystalline silica showed increases in sister chromatid exchange and chromosomal aberrations in peripheral blood lymphocytes. Most cellular genotoxicity studies with quartz gave negative results; however, *in vitro* exposure to some quartz samples caused micronucleus formation or cell transformation in several cell types, including Syrian hamster embryo cells, Chinese hamster lung cells, and human embryonic lung cells (IARC 1997).

Properties

Silica (SiO₂) is a group IV metal oxide that exists as colorless or white trigonal crystals and has a molecular weight of 60.1. It occurs naturally in crystalline and amorphous forms, and the specific gravity and melting point both depend on the crystalline form. The basic structural units of the silica mineral are silicon tetrahedra (SiO₄). Slight variations in the orientation of the tetrahedra result in the different polymorphs of silica; crystalline silica has seven polymorphs. In crystalline silica, silicon and oxygen atoms are arranged in definite regular patterns throughout (Parmeggiani 1983).

Quartz, cristobalite, and tridymite are the three most common crystalline forms of free silica (USBM 1992). Quartz is by far the most common; it is found abundantly in most rock types, including granites and quartzites, and in sands and soils. Cristobalite and tridymite are found in volcanic rocks. All three forms are interrelated and may change their form under different temperature and pressure conditions. The structure of quartz is more compact than that of tridymite or cristobalite (IARC 1987, 1997). Quartz melts to a glass, and its coefficient of expansion by heat is the lowest of any known substance. Silica is practically insoluble in water at 20°C and in most acids; but its solubility increases with temperature and pH and is affected by the presence of trace metals. The rate of solubility also is affected by particle size, and the external amorphous layer in quartz is more soluble than the crystalline underlying core. Silica dissolves readily in hydrofluoric acid, producing silicon tetrafluoride gas (Merck 1989, IARC 1997).

Use

Because of its unique physical and chemical properties, crystalline silica has many uses. Commercially produced silica products include quartzite, tripoli, ganister, chert, and novaculite. Crystalline silica also occurs in nature as agate, amethyst, chalcedony, cristobalite, flint, quartz, tridymite, and, in its most common form, sand (IARC 1997). Naturally occurring silica materials are classified by end use or industry. Sand and gravel are produced almost exclusively for road building and concrete construction, depending on particle size and shape, surface texture, and porosity (IARC 1987).

Silica sand deposits, commonly quartz or derived from quartz, typically have a silica content of 95%; however, impurities may be present at up to 25%. Silica sand has been used for many different

purposes over many years. In some instances, grinding of sand or gravel is required, increasing the levels of dust containing respirable crystalline silica. Sand with low iron content and more than 98% silica is used in the manufacture of glass and ceramics. Silica sand also is used in foundry castings, in abrasives (such as sandpaper and grinding and polishing agents), in sandblasting materials, in hydraulic fracturing to increase rock permeability to increase oil and gas recovery, as a raw material for the production of silicon and ferrosilicon metals, and as a filter for large volumes of water, such as in municipal water and sewage treatment plants (IARC 1997).

Extremely fine grades of silica sand products are known as flours. Silica flour, not always labeled as containing crystalline silica and often mislabeled as amorphous silica, is used industrially as abrasive cleaners and inert fillers. Silica flour may be used in toothpaste, scouring powders, metal polishes, paints, rubber, paper, plastics, wood fillers, cements, road surfacing materials, and foundry applications (NIOSH 1981). Cristobalite is a major component of refractory silica bricks; the high temperatures at which the bricks are fired convert the quartz mainly to cristobalite (IARC 1997).

Production

Silica used in commercial products is obtained mainly from natural sources (IARC 1997). U.S. production of silica sand (industrial sand and gravel combined) was estimated at 28.5 million metric tons (62.7 billion pounds) in 1997 and 27.9 million metric tons (61.4 billion pounds) in 2001 (Dolley 2008). U.S. production of high-purity quartz was 315,000 lb in 1979, decreasing to 174,000 lb in 1981, and rising to 800,000 lb in 1983 (IARC 1987). Natural quartz crystals are no longer mined in the United States. Synthetic quartz crystals (hypothermally cultured quartz crystals) now are used as the raw material for quartz production. The precursor material for synthetic quartz crystals is lasca (high-purity quartz dust), which was mined in the United States for many years; however, U.S. mining and processing of lasca ended in 1997. Lasca mining production was estimated at 1 million pounds in 1985 and 600,000 lb in 1988. In 2009, three U.S. firms produced cultured quartz crystals from imported and stockpiled lasca. No data on U.S. imports or exports of quartz crystal (industrial) were reported in 2009. Quartz-crystal import and export quantities and values reported in previous years included zirconia that was inadvertently reported as quartz crystal (Dolley 2009).

Exposure

Crystalline silica is an abundant and commonly found natural material. Human exposure to respirable crystalline silica, primarily quartz dust, occurs mainly in industrial and occupational settings. Non-occupational exposure to respirable crystalline silica results from natural processes and anthropogenic sources; silica is a common air contaminant. Residents near quarries and sand and gravel operations potentially are exposed to respirable crystalline silica. A major source of cristobalite and tridymite in the United States is volcanic rock in California and Colorado (NIOSH 1986). Local conditions, especially in deserts and areas around recent volcanic eruptions and mine dumps, can give rise to silica-containing dust (IARC 1987).

Consumers may be exposed to respirable crystalline silica from abrasives, sand paper, detergent, grouts, and concrete (IARC 1997). Crystalline silica may also be an unintentional contaminant; for example, diatomaceous earth, used as a filler in reconstituted tobacco sheets, may be converted to cristobalite as it passes through the burning tip of tobacco products (IARC 1987).

Respirable quartz levels exceeding 0.1 mg/m³ are most frequently found in metal, nonmetal, and coal mines and mills, granite quarrying and processing, crushed-stone and related industries, foundries, the

ceramics industry, construction, and sandblasting operations (IARC 1997). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 81,221 workers potentially were exposed to quartz (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 944,731 workers, including 112,888 women, potentially were exposed to quartz and that 31,369 workers, including 2,228 women, potentially were exposed to cristobalite (NIOSH 1990). The National Institute for Occupational Safety and Health (NIOSH 2002) estimated that 522,748 workers in nonmining industries and 722,708 workers in mining industries potentially were exposed to respirable crystalline silica in 1986.

Potential exposure to respirable crystalline silica has been studied in metal and nonmetal mining and milling operations. Workers in sandstone, clay, shale, and miscellaneous nonmetallic mineral mills had the highest exposure to silica dust. Within the mills, the workers with the highest exposure were baggers, general laborers, and personnel involved in the crushing, grinding, and sizing operations. Workers in the granite and stone industry and in construction also are potentially exposed to respirable crystalline silica. Potential exposure was highest for sculptors and carvers, stencil cutters, polishers, and sandblasters; for these occupations, the silica content of respirable dust ranged from 4.8% to 12.2%. Concentrations of respirable crystalline silica ranged from 0.01 to 0.20 mg/m³ in clay-pipe factories and from 0 to 0.18 mg/m³ in a plant producing ceramic electronic equipment parts. Silica concentrations of at least twice the permissible exposure limit were found in 10% of 348 air samples collected from glass-manufacturing industries and 23% to 26% of samples from clay-products and pottery industries. One third of samples from fibrous-glass plants had concentrations of respirable crystalline silica in excess of 0.10 mg/m³, and 23% of samples collected in iron and steel foundries had concentrations in excess of 0.20 mg/m³ (IARC 1987). Occupational exposure to cristobalite may occur in industries where silica products are heated, including refractory brick and diatomaceous earth plants and ceramic and pottery manufacturing plants (IARC 1997).

Regulations

Mine Safety and Health Administration

Silica sand or other materials containing more than 1% free silica shall not be used as an abrasive substance in abrasive blasting in underground areas and underground mines.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 250 mppcf/(%SiO₂ + 5), 10 mg/m³/(%SiO₂ + 2) for crystalline quartz (respirable); = 30 mg/m³/(%SiO₂ + 2) for quartz (total); = one half the value calculated from the count or mass formula for quartz for cristobalite and tridymite (mppcf = millions of particles per cubic foot).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.025 mg/m³ (respirable fraction).

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.05 mg/m³.

Immediately dangerous to life and health (IDLH) limit = 25 mg/m³ for cristobalite, tridymite; = 50 mg/m³ for quartz, tripoli.

Listed as a potential occupational carcinogen.

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Soots

CAS No.: none assigned

Known to be human carcinogens

First listed in the *First Annual Report on Carcinogens* (1980)

Carcinogenicity

Soots are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Exposure to soots was first associated with scrotal cancer (a rare tumor) among chimney sweeps in 1775. Numerous case reports and several epidemiological studies have since confirmed an increased risk of scrotal and other skin cancers among chimney sweeps. Cohort studies in several European countries found that chimney sweeps had significantly increased risks of mortality from lung cancer, and one study found increased risks of leukemia and cancer of the esophagus and liver. Although these studies did not control for the effects of smoking or alcohol consumption, these factors were not believed to have significantly biased the risk estimates (IARC 1985, 1987).

Since soots were reviewed for listing in the *First Annual Report on Carcinogens* and by the International Agency for Research on Cancer, follow-up studies of Swedish chimney sweeps reported increased risks of cancer at other tissue sites, including prostate, bladder, and total lymphatic and hematopoietic cancer. Risks of esophageal and lung cancer increased with increasing exposure, and risks of lung, bladder, and esophageal cancer remained elevated after adjustment for smoking. The risk of esophageal cancer also remained elevated after adjustment for alcohol consumption (Evanoff *et al.* 1993).

Cancer Studies in Experimental Animals

Dermal exposure of mice to several soot extracts, including those derived from combustion of household coal, oil shale, and heating oil produced from shale oil, caused skin tumors. In rats, intratracheal administration of an extract of soot from the combustion of oil shale caused lung tumors. Subcutaneous implants of wood soot caused a few tumors (sarcoma) at the implantation site in female rats, but implants in the scrotal sac did not cause tumors in male rats (IARC 1985, 1987). Studies of coal soot (whole-body exposure), wood-soot extract (dermal exposure), and extract of fuel-oil soot (dermal exposure) in rodents were inadequate for evaluation of carcinogenicity. IARC (1987) concluded that there was sufficient evidence for the

carcinogenicity of soot extracts but insufficient evidence for the carcinogenicity of soots in experimental animals.

Additional Information Relevant to Carcinogenicity

Soots are known to contain a number of known and potentially carcinogenic chemicals, including arsenic, cadmium, chromium, nickel, and several polycyclic aromatic hydrocarbons (PAHs), including benz[*a*]anthracene, benzo[*a*]pyrene, dibenz[*a,h*]anthracene, and indeno[1,2,3-*cd*]pyrene.

Properties

Soots are black particulate matter formed as by-products of combustion or pyrolysis of organic (carbon-containing) materials, such as coal, wood, fuel oil, waste oil, paper, plastics, and household refuse. Their chemical compositions and properties are highly variable and depend on the type of starting material and the combustion conditions. Soots vary with respect to their relative amounts of carbon; their particle types, sizes, and shapes; and the types of organic and inorganic compounds adsorbed to the particles. In general, soots have a total carbon content exceeding 60% and a high content of inorganic material and/or soluble organic fraction. The soluble organic fraction of soot is extractable with organic solvents and consists of PAHs and their derivatives. Inorganic constituents may include oxides, salts, metals, sulfur and nitrogen compounds, water, and other adsorbed liquids and gases (IARC 1985, Watson and Valberg 2001).

Soots are classified into four morphologically distinct forms: (1) aciniform carbon, (2) carbonaceous xerogel particles, (3) carbon cenospheres, and (4) coke and char fragments. Aciniform carbon consists of aggregates of rounded particles fused together in random configurations, said to resemble grape clusters. Although particulate emissions from fireplaces consist largely of aciniform carbon, this form is uncommon in chimney soot. Xerogel particles form when organic materials deposited on aciniform carbon are heated, causing the particulate aggregates to be cemented together; this form is common in chimney soot. Carbon cenospheres are hard, shiny, porous or hollow spheres formed when carbonaceous liquid droplets undergo carbonization with little change in shape; they are particularly associated with combustion of heavy fuel-oil sprays. Coke and char fragments consist of carbonized wood or coal and range in size from microns to millimeters; they are common in chimney soots from wood- or coal-burning fireplaces (IARC 1985).

Use

As unwanted by-products, soots have limited uses. They have been used in horticulture and in recovery of trace metals in the metallurgical industry. Weathered soot has been used as a fertilizer to provide small amounts of nitrogen and essential trace metals to plants. Soot has also been used horticulturally as a slug deterrent and as a soil conditioner to increase heat absorption by darkening the soil (IARC 1985).

Production

Soots are not produced commercially. They are by-products of the incomplete combustion or pyrolysis of organic materials (IARC 1985).

Exposure

Humans may be exposed to soots by inhalation, ingestion, or dermal contact. The general population potentially is exposed to soots from fireplaces, furnaces, engine exhaust, and particulate emissions from any combustion source. Occupational exposure to soot may occur among chimney sweeps, heating-unit service personnel, brick masons and helpers, building demolition personnel, insulators, firefighters,

metallurgical workers, horticulturists, and anyone who works where organic materials are burned. Chimney sweeps likely have the highest occupational exposure to soots. In 1982, there were an estimated 5,000 chimney sweeps in the United States. In addition to cleaning residential house chimneys, chimney sweeps clean industrial chimneys and boilers and are exposed to both gaseous and particulate combustion products. Soot concentrations to which they are exposed vary depending on the sweeping duties, type of chimney, and type of fuel. In a Danish study, soot concentrations from personal samplers ranged from 4.1 to 388 µg/L for total soot and 1.1 to 25 µg/L for respirable soot. The highest concentrations were measured in chimney ducts where coal was burned and in chimneys where wood and other fuels were burned (IARC 1985).

Regulations

No regulations or guidelines relevant to reduction of exposure specifically to soots were identified.

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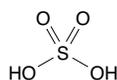
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Strong Inorganic Acid Mists Containing Sulfuric Acid

CAS No. 7664-93-9 (Sulfuric acid)

Known to be human carcinogens

First listed in the *Ninth Report on Carcinogens* (2000)



Sulfuric acid

Carcinogenicity

Strong inorganic acid mists containing sulfuric acid are *known to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Occupational exposure to strong inorganic acid mists containing sulfuric acid is specifically associated with laryngeal and lung cancer. Studies of one U.S. cohort of male workers in pickling operations in the steel industry found excesses of laryngeal cancer (approximately twofold) after adjustment for smoking and other potentially confounding variables (Steenland *et al.* 1988). A ten-year follow-up of this cohort also found a twofold excess of laryngeal cancer, consistent with the earlier findings (Steenland 1997). The same cohort showed an excess of lung cancer after adjustment for smoking and other potentially confounding variables (Steenland and Beaumont 1989). A nested case-control study of workers in a U.S. petrochemical plant found a dose-related increase in the risk of laryngeal cancer among workers exposed to sulfuric acid at moderate levels (odds ratio [OR] = 4.6; 95% confidence interval [CI] = 0.83 to 25.35) or high

levels (OR = 13.4; 95% CI = 2.08 to 85.99) (Soskolne *et al.* 1984). A Canadian population-based case-control study also found a dose-related risk of laryngeal cancer for workers exposed to sulfuric acid mist, after controlling for tobacco and alcohol use and using only the most specific exposure scale (Soskolne *et al.* 1992). A similar Canadian population-based case-control study suggested an increased risk of lung cancer (oat-cell carcinoma) (Siemiatycki 1991).

Additional Information Relevant to Carcinogenicity

The manufacture of isopropyl alcohol by the strong-acid process, which uses sulfuric acid, has been classified by the International Agency for Research on Cancer as carcinogenic to humans, based on increased incidence of cancer of the paranasal sinuses in workers (IARC 1977). The carcinogenic activity of sulfuric acid is most likely related to the genotoxicity of low-pH environments, which are known to increase the rates of depurination of DNA and deamination of cytidine (IARC 1992a).

Cancer Studies in Experimental Animals

No adequate studies in experimental animals of the carcinogenicity of sulfuric acid or strong inorganic acid mists containing sulfuric acid have been reported in the literature.

Properties

Sulfuric acid is a strong acid that is a clear, colorless oily liquid at room temperature. Impure or spent sulfuric acid is a dark-brown to black liquid. Sulfuric acid is soluble in water and ethanol and is very corrosive (IARC 1992b). Physical and chemical properties of sulfuric acid are listed in the following table.

Property	Information
Molecular weight	98.1 ^a
Density	1.8 g/cm ^{3a}
Melting point	10.31°C ^a
Boiling point	290°C ^a
Log <i>K</i> _{ow}	1.92 ^b
Vapor pressure	5.93 × 10 ⁻⁵ mm Hg at 25°C ^a
Vapor density relative to air	3.4 ^a
Dissociation constant (p <i>K</i> _a)	1.98 at 25°C ^a

Sources: ^aHSDB 2009, ^bATSDR 1998.

A mist is defined as a liquid aerosol formed by condensation of a vapor or by atomization of a liquid. Strong inorganic acid mists containing sulfuric acid may be generated during a process when factors such as evaporation, solution strength, temperature, and pressure combine to result in release of a mist (IARC 1992a). Sulfuric acid mists are the most extensively studied of the acid mists. Liquid sulfuric acid may exist in air as a vapor or a mist; however, it exists most often as mist, because of its low volatility and high affinity for water.

Acid strength is based on the position of equilibrium in an acid-base reaction and is measured by the negative logarithm (to the base 10) of the acid dissociation constant (p*K*_a). The lower the p*K*_a, the stronger the acid. Sulfuric acid has two p*K*_a values because it releases two hydrogen atoms in aqueous solution, but the first p*K*_a cannot be measured accurately and is reported as less than 0. Dehydration occurs because sulfuric acid has a strong affinity for water. It forms various hydrates when in contact with organic matter or water vapor. Although it is miscible with water, contact with water generates heat and may produce a violent reaction. The reaction with water releases toxic and corrosive fumes and mists. Sulfuric acid is noncombustible, but it can release flammable hydrogen gas when in contact with metals. Thermal decomposition to sulfur trioxide and water occurs at 340°C. Sulfuric acids are available in the following grades: commer-

cial, electrolyte (high purity), textile (low organic content), and chemically pure or reagent grades (IARC 1992b, ATSDR 1998, HSDB 2009).

Sulfur trioxide is added to sulfuric acid to produce fuming sulfuric acid (also known as oleum). Oleum has a molecular weight of 178.1, may contain up to 80% free sulfur trioxide, and is a colorless to slightly colored oily liquid. Sulfur trioxide has a molecular weight of 80.1 and can exist as a gas, liquid, or solid. Liquid sulfur trioxide is colorless and fumes in air at ambient conditions. In the presence of moisture, sulfur trioxide forms solid polymers consisting of alpha and beta forms. The melting points of the alpha (62.3°C) and beta (32.5°C) forms are the temperatures at which they depolymerize back to the liquid form. The liquid form has a boiling point of 44.8°C and a density of 1.92 g/cm³ at 20°C. Both oleum and sulfur trioxide react with water and water vapor to form sulfuric acid mists. Oleum is available in several grades with free sulfur trioxide content ranging from 20% to 99.9% and corresponding sulfuric acid equivalents ranging from 104.5% to 122.5%. Sulfur trioxide is available with a minimum purity of 99.5% as a stabilized technical grade or unstabilized liquid (IARC 1992b).

Use

Strong inorganic acid mists containing sulfuric acid are not used *per se* in industry or in commercial products but are generated from both natural and industrial sources. In particular, sulfuric acid mists may be produced during the manufacture or use of sulfuric acid, sulfur trioxide, or oleum. Sulfur trioxide is primarily used to make sulfuric acid, but it is also used as a sulfonating or oxidizing agent. Oleum is used as a sulfonating or dehydrating agent, in petroleum refining, and as a laboratory reagent. Sulfuric acid is one of the most widely used industrial chemicals; however, most of it is used as a reagent rather than an ingredient. Therefore, most of the sulfuric acid used ends up as a spent acid or a sulfate waste. Exact purity grades are required for use in storage batteries and for the rayon, dye, and pharmaceutical industries. Sulfuric acids used in the steel, chemical, and fertilizer industries have less exacting standards (IARC 1992b, ATSDR 1998, HSDB 2009).

Sulfuric acid is used in the following industries: fertilizer, petroleum refining, mining and metallurgy, ore processing, inorganic and organic chemicals, synthetic rubber and plastics, pulp and paper, soap and detergents, water treatment, cellulose fibers and films, and inorganic pigments and paints. Between 60% and 70% of the sulfuric acid used in the United States is used by the fertilizer industry to convert phosphate rock to phosphoric acid. All other individual uses account for less than 1% to less than 10% of the total consumption. Sulfuric acid use is declining in some industries. There is a trend in the steel industry to use hydrochloric acid instead of sulfuric acid in pickling, and hydrofluoric acid has replaced sulfuric acid for some uses in the petroleum industry. The primary consumer product that contains sulfuric acid is the lead-acid battery; however, this accounts for a small fraction of the overall use. Sulfuric acid is also used as a general-purpose food additive (IARC 1992b, ATSDR 1998).

Production

Strong inorganic acid mists containing sulfuric acid may be produced as a result of the use of mixtures of strong inorganic acids, including sulfuric acid, in industrial processes such as acid treatment of metals, phosphate fertilizer manufacture, and lead battery manufacture (IARC 1992b). The degree of vapor or mist evolution varies with the process and method. In pickling, for instance, mist may escape from acid tanks when hydrogen bubbles and steam rise from the surface of the solution.

Sulfuric acid is the largest-volume chemical produced in the United States (CEN 1996). Annual production increased from 28.3 million metric tons (62.4 billion pounds) in 1972 to 40.1 million metric tons (88.4 billion pounds) in 1980 (IARC 1992b, ATSDR 1998). Between 1981 and 2002, annual production remained fairly steady, ranging from a low of 32.6 million metric tons (71.9 billion pounds) in 1986 (IARC 1992b) to a high of 44 million metric tons (97 billion pounds) in 1998 (CEN 2003). Between 1992 and 2002, annual production declined by only 1% (CEN 2003). Many different grades and strengths of sulfuric acid are produced. The primary method of production is the contact process, which consists of the following steps: (1) oxidation of sulfur to sulfur dioxide, (2) cooling of the gases, (3) oxidation of sulfur dioxide to sulfur trioxide, (4) cooling of the sulfur trioxide gas, and (5) addition of sulfur trioxide to water to produce sulfuric acid. Oleum is produced at sulfuric acid plants by adding sulfur trioxide to sulfuric acid. In addition to primary production, large quantities of spent sulfuric acid are reprocessed (IARC 1992b, ATSDR 1998). In 2009, sulfuric acid was available from 76 U.S. suppliers, and oleum from 6 U.S. suppliers (ChemSources 2009).

The United States is a net importer of sulfuric acid and oleum. U.S. imports were 275,000 metric tons (600 million pounds) in 1975, 426,000 metric tons (940 million pounds) in 1984, and 2.3 million metric tons (5 billion pounds) in 1993, and exports were 129,000 metric tons (284 million pounds) in 1975, 119,000 metric tons (262 million pounds) in 1984, and 136,000 metric tons (300 million pounds) in 1993 (HSDB 2009). In 2009, imports were about 5 million kilograms (11 million pounds), and exports were 262,000 kg (578,000 lb) (USITC 2009).

Exposure

Human exposure to strong inorganic acid mists containing sulfuric acid may occur by inhalation, ingestion, or dermal contact. Exposure depends on many factors, including particle size, proximity to the source, and control measures such as ventilation and containment. Data on particle size distribution of acid mists are limited, and sampling methods have generally not differentiated between liquid and gaseous forms of acids. One study of sulfuric acid mists in several U.S. battery manufacturing plants found that particles had a mass median aerodynamic diameter of 5 to 6 µm, which indicates that sulfuric acid mists contain aerosol particles that can be deposited in both the upper and lower airways (IARC 1992a).

Sulfuric acid and mists and vapors containing sulfuric acid are present in the environment because of releases of sulfur compounds from both natural and anthropogenic sources. Volcanic eruptions, biogenic gas emissions, and oceans are the primary natural sources of sulfur emissions. Volcanoes release 0.75 million to 42 million metric tons (1.7 billion to 93 billion pounds) of sulfur per year, and airborne sea spray and marine organisms release between 12 million and 15 million metric tons per year (26 billion to 33 billion pounds). Coal combustion by electric plants is the major anthropogenic source of sulfur dioxide release. Sulfur dioxide emissions in the United States declined by more than 60% from the early 1970s (28 million metric tons [62 billion pounds]) to 1994 (18 million metric tons [40 billion pounds]) and decreased by another 13% from 1994 to 1995 (ATSDR 1998).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of sulfuric acid fluctuated from year to year, but remained in the range of 26 million to 197 million pounds from 1994 and 2007. In 2007, 840 facilities released over 138.5 million pounds of sulfuric acid, of which over 99% was released to air (TRI 2009). Ambient air may contain particulate-associated mixtures of sulfuric acid and ammonium sulfates (sulfuric acid

partially or completely neutralized by atmospheric ammonia). The relative amounts of sulfuric acid and total sulfates depend on meteorological and chemical parameters. The presence of sulfuric acid and sulfates in the atmosphere is believed to be due to oxidation of sulfur dioxide in cloud water and other atmospheric media. Ambient-air concentrations of sulfuric acid are at least an order of magnitude lower than concentrations in occupational settings (IARC 1992a).

The industries in which occupational exposure to strong acid mists may occur include chemical manufacture (sulfuric acid, nitric acid, synthetic ethanol, and vinyl chloride), building and construction, manufacture of lead-acid batteries, manufacture of phosphate fertilizers, pickling and other acid treatments of metals, manufacture of petroleum and coal products, oil and gas extraction, printing and publishing, manufacture of paper and allied products, and tanneries. Most of the available occupational exposure data comes from the pickling and plating industries. In the 1970s and 1980s, average concentrations of strong inorganic acid mists containing sulfuric acid in workplace air were less than 0.01 to 7.3 mg/m³ for pickling and acid cleaning, less than 0.07 to 0.57 mg/m³ for phosphate fertilizer manufacture, 0.01 to 1.03 mg/m³ for lead battery manufacture, and less than 0.005 to 0.5 mg/m³ for other industries (IARC 1992a).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 499,446 workers were exposed to sulfuric acid, 824,985 to hydrochloric acid, 132,401 to nitric acid, and 454,920 to phosphoric acid (NIOSH 1976). The National Occupational Exposure Survey (conducted from 1981 to 1983), which reported on more than 54,500 plants with potential workplace exposure to strong inorganic acids, estimated that 775,587 workers, including 173,653 women, potentially were exposed to sulfuric acid; 1,238,572 workers, including 388,130 women, to hydrochloric acid; 297,627 workers, including 76,316 women, to nitric acid; and 1,256,907 workers, including 450,478 women, to phosphoric acid (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of sulfuric acid on ships and barges.

Consumer Product Safety Commission (CPSC)

Sulfuric acid and any preparation containing sulfuric acid in a concentration of 10% or more must have a label containing the word "poison."

Department of Transportation (DOT)

Sulfuric acid and numerous sulfuric acid mixtures are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Standards of performance have been established for sulfuric acid production units, including a limit on acid mist (expressed as H₂SO₄) emissions of 0.15 lb/ton of acid produced.

Clean Water Act

Sulfuric acid is designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb for sulfuric acid.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Aerosol forms of sulfuric acid are listed and thus subject to reporting requirements.

Threshold planning quantity (TPQ) = 1,000 lb for sulfuric acid.

Reportable quantity (RQ) = 1,000 lb for sulfuric acid.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of sulfuric acid = U103, P115.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 mg/m³ for sulfuric acid.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.2 mg/m³ for sulfuric acid contained in strong inorganic acid mists.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 mg/m³ for sulfuric acid.

Immediately dangerous to life and health (IDLH) limit = 15 mg/m³ for sulfuric acid.

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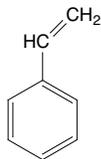
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Styrene

CAS No. 100-42-5

Reasonably anticipated to be a human carcinogen

First listed in the *Twelfth Report on Carcinogens* (2011)



Carcinogenicity

Styrene is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis.

Cancer Studies in Humans

The limited evidence for the carcinogenicity of styrene in humans is based on studies of workers exposed to styrene that showed (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers. Elevated risks of lymphohematopoietic cancer were found among workers with higher exposure to styrene after an appropriate elapsed time since first exposure. In some studies, the risks increased with increasing measures of exposure, such as average exposure, cumulative exposure, or number of years since first exposure. However, the types of lymphohematopoietic cancer observed in excess varied across different cohort studies, and excess risks were not found in all cohorts. There is also some evidence for increased risks of esophageal and pancreatic cancer among styrene-exposed workers. Causality is not established, as the possibility that the results were due to chance or to confounding by exposure to other carcinogenic chemicals cannot be completely ruled out. However, a causal relationship between styrene exposure and cancer in humans is credible and is supported by the finding of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers.

Most of the evidence in humans comes from occupational cohort studies in two major industries: (1) the reinforced-plastics industry and (2) the styrene-butadiene rubber industry. Studies of workers in a third industry, the styrene monomer and polymer industry, were not considered to be as informative, because they were limited by small numbers of cancer cases among exposed workers, and there was potential confounding by coexposure to benzene. Workers in the reinforced-plastics industry were exposed to the highest levels of styrene, and they had few other potentially carcinogenic exposures. However, the majority of the workers had short periods of employment. In the styrene-butadiene rubber industry, workers were exposed to lower levels of styrene than in the reinforced-plastics industry, but a large number of workers studied had long-enough follow-up times to permit detailed analysis of the incidences of lymphohematopoietic cancers. The main limitation of the studies in styrene-butadiene rubber workers is potential confounding by other exposures, principally to butadiene, which is a known human carcinogen associated with increased risk of leukemia (Grosse *et al.* 2007, NTP 2004a); exposures to butadiene and styrene are highly correlated in this industry.

The most informative studies in the reinforced-plastics industry were the two largest cohort studies: a Danish cohort of male workers (Kolstad *et al.* 1994, 1995) and a European multinational mortal-

ity cohort of predominantly male workers, which included a subset of the Danish workers (Kogevinas *et al.* 1994). In the styrene-butadiene industry, the major study was a large multi-plant cohort mortality study of male styrene-butadiene rubber workers in the United States and Canada (Graff *et al.* 2005, Delzell *et al.* 2006), which encompassed most of the workers from two earlier cohorts (a small study by Meinhardt *et al.* 1978 and a larger study by Matanoski *et al.* 1990). The studies in both industries included internal analyses (using unexposed members of the cohort as the comparison group); such analyses are less susceptible to confounding than those using external reference populations. Internal analyses were used to evaluate exposure-response relationships for cumulative exposure, average exposure, peak exposure (a measure of exposure intensity), or time since first exposure in the multinational cohort study of reinforced-plastics workers (Kogevinas *et al.* 1994) and in the multi-plant study of styrene-butadiene workers (Delzell *et al.* 2006). Without *a priori* knowledge, it is difficult to know which exposure metric is most appropriate for evaluating causality, so a positive relationship observed with any exposure metric is a concern. The studies also conducted standardized mortality ratio (SMR) or standardized incidence ratio (SIR) analyses, which compared observed with expected numbers of events (deaths or incident cases) based on national mortality or incidence rates. Two additional cohort studies of U.S. reinforced-plastics workers were less informative. A study by Ruder *et al.* (2004) had limited statistical power to detect positive associations between styrene exposure and uncommon types of cancer. A study by Wong *et al.* (1994) had a relatively large cohort and conducted internal analyses; however, the internal analyses were limited to exposure duration and cumulative exposure.

Lymphohematopoietic Cancer

Increased risks for leukemia, lymphoma, or all lymphohematopoietic cancer were found among styrene-exposed workers in both the reinforced-plastics and styrene-butadiene rubber industries. The evidence comes primarily from positive exposure-response relationships found in the multinational European study (reinforced-plastics workers) (Kogevinas *et al.* 1994) and the multi-plant cohort study of styrene-butadiene workers (Delzell *et al.* 2006) and is supported by findings of increased cancer risks among subgroups of workers with higher levels of styrene exposure or longer times since first exposure (Kogevinas *et al.* 1994, Kolstad *et al.* 1994). Although coexposure to butadiene is a concern in the styrene-butadiene industry, the finding of increased cancer risk in the reinforced-plastics industry, where such confounding is not an issue, suggests that styrene is a potential risk factor for lymphohematopoietic cancer. The types of lymphohematopoietic cancer observed in excess varied across different cohorts; a similar pattern has been observed for other epoxide-forming substances, such as 1,3-butadiene and ethylene oxide (see the profiles for those substances). Moreover, it is difficult to compare the risks for specific types of lymphohematopoietic cancer across studies, because (1) these cancers may have been grouped differently between studies or in the same study between different types of analyses (e.g., external and internal analyses in the study by Wong *et al.* 1994), (2) diagnoses based on death certificates may be inaccurate, and (3) lymphohematopoietic cancer classification and groupings have changed over time. In general, these limitations make it more difficult to see consistent associations between styrene exposure and specific types of lymphohematopoietic cancer across studies.

Reinforced-Plastics Industry

In the multinational study of reinforced-plastics workers, workers in the two highest categories of average styrene exposure had

significantly higher risks (or elevated risks approaching statistical significance) than did workers in the lowest exposure group for all lymphohematopoietic cancer (relative risk [RR] = 3.08, 95% confidence interval [CI] = 1.04 to 9.08, 13 cases with exposure of 120 to 199 ppm; RR = 3.59, 95% CI = 0.98 to 13.14, 8 cases with exposure \geq 200 ppm). In addition, the risk of malignant lymphoma was significantly elevated in the second-highest exposure group (RR = 7.15, 95% CI = 1.21 to 42.11, 8 exposed cases). A fourfold higher risk of malignant lymphoma was also found for the highest-exposure group, but it was based on small numbers of exposed cases and was not statistically significant. Risks increased with increasing average exposure for all lymphohematopoietic cancer ($P_{\text{trend}} = 0.019$) and for malignant lymphoma ($P_{\text{trend}} = 0.052$). Time since first hire also was associated with lymphohematopoietic cancer ($P_{\text{trend}} = 0.012$) and malignant lymphoma ($P_{\text{trend}} = 0.072$); risk estimates for workers with the longest time since first hire compared with workers with the shortest time since first hire were 3.97 (95% CI = 1.30 to 12.13, 9 exposed cases) for all lymphohematopoietic cancer and 5.16 (95% CI = 0.90 to 29.47, 4 exposed cases) for malignant lymphoma (Kogevinas *et al.* 1994). No significant relationship with cumulative exposure was observed, although statistically nonsignificant elevated risks for lymphoma were found for all groups with cumulative exposure greater than 75 ppm. The proportion of short-term workers was higher among the workers with the highest exposure levels (laminators); therefore, measures of exposure intensity (such as average exposure level) may be more informative than measures of exposure duration for evaluating risks.

Among Danish reinforced-plastics workers, the incidence of leukemia was significantly elevated for workers with earlier dates of first exposure (1964 to 1970, during which time the highest exposure levels occurred) (Kolstad *et al.* 1994). Significantly elevated risks were also found among workers with at least ten years since first employment; within this group, the increased risks were concentrated among short-term workers (those workers with exposure duration of less than one year). The findings for leukemia were similar in the internal analyses using unexposed workers as controls for short-term workers, thus helping to rule out confounding by socioeconomic status or lifestyle factors of the short-term workers.

Neither of the two U.S. cohort studies of reinforced-plastics workers found a significant association between styrene exposure and lymphohematopoietic cancer; however, neither study evaluated risk by average exposure intensity, and the smaller study (Ruder *et al.* 2004) had very limited statistical power to detect an association. In the larger U.S. study (Wong *et al.* 1994), no association was found between cumulative exposure or duration of exposure and all lymphohematopoietic cancer, non-Hodgkin's lymphoma, or leukemia. The analysis included both exposure measures, which are highly correlated with each other; this may have reduced the statistical power to detect an association (IARC 2002).

Styrene-Butadiene Rubber Industry

The multi-plant cohort study of male styrene-butadiene rubber workers found significantly increased risks (SMRs) of non-Hodgkin's lymphoma (NHL), NHL-chronic lymphocytic leukemia (NHL-CLL), and leukemia (overall and specific types) among subgroups of workers with long duration of employment ($>$ 10 years) and long time since first exposure (20 to 29 years or \geq 30 years), in specific job categories, and with the highest levels of cumulative exposure to styrene (Graff *et al.* 2005, Sathiakumar *et al.* 2005, Delzell *et al.* 2006).

In an attempt to disentangle the effects of styrene from those of butadiene, internal analyses were conducted for quartiles of cumulative exposure or exposure to periodic spikes of high styrene concentrations (styrene peaks, defined as \geq 50 ppm) involving statistical

models with (1) styrene exposure only, (2) styrene and butadiene exposure, and (3) styrene and butadiene exposure plus dermal exposure to dimethyldithiocarbamate (DMDTC). (The relevance of including DMDTC in these models is not clear, because there is no independent evidence that DMDTC is carcinogenic in animals or humans.) The number of cases at each exposure level was small, which limited the power to detect statistically significant risk estimates. No trend analyses were reported. The analyses suggested an exposure-response relationship between NHL and NHL-CLL combined and exposure to styrene that was not explained by exposure to butadiene. The relative risk of NHL or NHL-CLL increased with increasing level of cumulative exposure to styrene and was not attenuated by control for butadiene exposure. However, the relative risk reached statistical significance only for the highest styrene exposure level in the styrene-only model and only for NHL-CLL combined. Exposure to butadiene was not associated with risk of NHL or NHL-CLL (Graff *et al.* 2005, Delzell *et al.* 2006).

Evidence for an association between styrene exposure and leukemia comes from analyses of cancer among workers exposed to styrene peaks. The relative risk of leukemia increased with exposure to increasing numbers of styrene peaks in all three chemical models and was significantly elevated at the two highest styrene exposure levels with control for butadiene exposure. The relative risk of leukemia also increased with increasing cumulative styrene exposure, but the response was attenuated by control for butadiene exposure, and no association remained after additional control for DMDTC.

A nested case-control study from the Matanoski cohort also found significantly increased risks of all lymphohematopoietic cancer ($P = 0.001$) and of lymphoma ($P = 0.020$) (International Classification of Disease codes 200 and 202, which are the same codes as for NHL) with exposure to styrene (1-ppm time-weighted average, compared with 0 ppm) in a statistical model that accounted for exposure to butadiene. Although the study population overlapped with that of the multi-plant cohort, it provided supporting evidence for the increased risk of lymphoma reported by Delzell *et al.*, because it used a different exposure assessment (based on measurements) and a different statistical model (Matanoski *et al.* 1997).

Cancer at Other Tissue Sites

Studies in the reinforced-plastics industry provided evidence that suggests a possible association between styrene exposure and cancer of the esophagus or pancreas. Mortality from esophageal cancer was increased in two of the four studies (Ruder *et al.* 2004, Wong *et al.* 1994), and a third study found a statistically nonsignificant increased risk among the workers with higher cumulative exposure (Kogevinas *et al.* 1994). For pancreatic cancer, increased risks were suggested in the cohort studies. Internal analyses of the Danish cohort found a significant risk of pancreatic cancer (incidence) among workers classified as having "probable high exposure" (Kolstad *et al.* 1995). Statistically nonsignificant increased risks of pancreatic cancer mortality were reported by the two U.S. cohort studies (Ruder *et al.* 2004, Wong *et al.* 1994) and for workers with higher cumulative exposure in the European study (Kogevinas *et al.* 1994). There was some evidence of an exposure-response relationship for pancreatic cancer; cancer risk increased with increasing cumulative exposure in the European multi-plant cohort ($P_{\text{trend}} = 0.068$) (Kogevinas *et al.* 1993, 1994). No excess mortality from esophageal or pancreatic cancer was found in studies of styrene-butadiene rubber workers; however, the only analysis reported was the SMR for the entire multi-plant cohort (Delzell *et al.* 2006).

Genetic Damage

DNA adducts (primarily, N²-guanine and O⁶-guanine, but also β N1-adenine adducts) were found in circulating white blood cells in many studies of styrene-exposed workers employed mainly in the reinforced-plastics industry; levels of O⁶-guanine were five- to seven-fold higher among styrene-exposed workers than controls (Vodicka *et al.* 2006a, Boffetta *et al.* 2009). In most studies in workers, single-strand DNA breaks showed exposure-related increases (Brenner *et al.* 1991, Maki-Paakkanen *et al.* 1991, Vodicka *et al.* 2006a). A meta-analysis of 22 studies found a positive association (weighted frequency ratio = 2.18, 95% CI = 1.52 to 3.13) between styrene exposure level and chromosomal aberration frequency when exposure levels were dichotomized as greater than or less than a threshold value of 30 ppm for an 8-hour time-weighted average (Bonassi *et al.* 1996).

Cancer Studies in Experimental Animals

Styrene caused lung tumors in several strains of mice and by two different routes of exposure. The most robust studies are two-year studies of inhalation exposure in CD-1 mice (Cruzan *et al.* 2001) and oral exposure (by stomach tube) in B6C3F₁ mice (NCI 1979). Inhalation exposure caused benign lung tumors (alveolar/bronchiolar adenoma) and increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma) in CD-1 mice of both sexes; in females, it also increased the separate incidence of malignant lung tumors. In male B6C3F₁ mice, oral exposure to styrene increased the combined incidence of benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma), and a positive dose-response trend was observed (NCI 1979).

These findings are supported by findings of lung tumors in both sexes of O20 mice exposed to styrene (Ponomarev and Tomatis 1978). In O20 mice, a single dose of styrene was administered to pregnant dams on gestational day 17, and pups were exposed orally once a week for 16 weeks after weaning. A significantly increased incidence and earlier onset of benign and malignant lung tumors combined (adenoma and carcinoma) occurred in mice of both sexes as early as 16 weeks after weaning. In a similar study with C57Bl mice administered a much lower dose of styrene, lung-tumor incidence was not significantly increased. In short-term studies, oral exposure to styrene caused cytotoxicity and increased cell replication in the mouse lung, supporting the findings of lung tumors following oral exposure to styrene in longer-term studies (Green *et al.* 2001).

The evidence from studies in rats is insufficient for reaching a conclusion concerning the carcinogenicity of styrene. Lung tumors were not observed in rats (IARC 2002); however, findings for mammary-gland tumors were equivocal. The incidence of mammary-gland tumors was increased in female Sprague-Dawley rats exposed to styrene in the drinking water (mammary fibroadenoma; Huff 1984) or by inhalation (malignant tumors; Conti *et al.* 1988), but decreased incidences of mammary-gland tumors (adenocarcinoma) were reported in another inhalation-exposure study of rats of the same strain (Cruzan *et al.* 1998).

Metabolism of Styrene

Styrene can be absorbed and widely distributed throughout the body through inhalation, ingestion, or skin contact, but the most important route of occupational exposure is inhalation (IARC 2002). Styrene is metabolized primarily (over 90%) to the genotoxic metabolite styrene-7,8-oxide, which can be detoxified by glutathione conjugation or conversion to styrene glycol by microsomal epoxide hydrolase. Pharmacokinetic models predict the concentration of styrene in the lung (Filser *et al.* 2002) or terminal bronchioles (Sarangapani *et al.* 2002) to be higher in mice than in rats and higher in rats than in humans. Sys-

temic distribution of styrene-7,8-oxide in workers has been demonstrated from measurements of styrene-7,8-oxide-based hemoglobin adducts in erythrocytes and DNA adducts in lymphocytes (Tornero-Velez *et al.* 2001, Vodicka *et al.* 2003, 2006a). Further oxidation of styrene glycol produces mandelic acid and phenylglyoxylic acid, the major metabolites identified in the urine of styrene-exposed workers (Manini *et al.* 2002). Because styrene-7,8-oxide contains a chiral carbon, it and some subsequent styrene metabolites can exist as either R or S enantiomers. A second, minor pathway of styrene metabolism involves oxidation of the aromatic ring resulting in formation of 4-vinylphenol, presumably via the arene intermediate styrene-3,4-oxide, which has been detected in humans (Pfäffli *et al.* 1981, Manini *et al.* 2003) and rats (Bakke and Scheline 1970) and whose occurrence in mice *in vivo* was implicated by indirect measures (Boogaard *et al.* 2000).

Styrene is metabolized primarily in the liver and the lung. In mice, the Clara cell is regarded as the major lung-cell type in which styrene is activated to styrene-7,8-oxide following inhalation exposure (Hynes *et al.* 1999). The initial step in styrene metabolism is catalyzed by cytochromes P450, and there are tissue-specific differences in the enzymes responsible for styrene oxidation. In mice, Cyp2e1 predominates in the liver, and Cyp2f2 in the lung (Carlson 1997, 2004, Vodicka *et al.* 2006a). In humans, CYP2A13, CYP2F1, CYP1A2, CYP2C8, CYP2A6, and CYP2E1 are active in metabolizing styrene to styrene glycol in the lung, and CYP2B6 and CYP2E1 are most active in the liver (Nakajima *et al.* 1994, IARC 2002, Fukami *et al.* 2008). Human CYP2F1 (equivalent to Cyp2f2 in mice and CYP2F4 in rats) has been shown to metabolize styrene *in vitro* (Nakajima *et al.* 1994). In general, expression of CYP enzymes is more widely distributed in the human lung than in the lungs of experimental animals, where expression is concentrated in Clara cells, type II alveolar cells, and alveolar macrophages. CYP2B6 is expressed in human Clara cells, and CYP2E1 in human bronchial, bronchiolar, and alveolar epithelium, alveolar macrophages, and lung tumors (Kivistö *et al.* 1995, Hukkanen *et al.* 2002). CYP2E1 is also expressed in lymphocytes (Siest *et al.* 2008), and CYP2E1 protein and activity were detected in human hematopoietic stem cells (Kousalova *et al.* 2004).

Because many of the enzymes involved in styrene metabolism are polymorphic, individuals may differ in their susceptibility to styrene-induced toxicity. Some studies have found that polymorphisms in glutathione S-transferase mu 1 influence excretion of styrene metabolites (De Palma *et al.* 2001, Haufroid *et al.* 2002, Teixeira *et al.* 2004); however, studies evaluating genotoxicity and polymorphisms in genes involved in either styrene metabolism or DNA repair have not clearly identified specific polymorphisms related to genotoxic effects (Godderis *et al.* 2006, Migliore *et al.* 2006, reviewed by Vodicka *et al.* 2006a).

Studies on Mechanisms of Carcinogenesis

The mechanisms of styrene carcinogenicity are not fully understood. The primary metabolite of styrene, styrene-7,8-oxide, is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* based on sufficient evidence in experimental animals. Oral exposure to styrene-7,8-oxide caused forestomach tumors in rats and mice and liver tumors in male mice (see the profile for styrene-7,8-oxide, NTP 2004b).

The proposed mechanisms for the carcinogenicity of styrene include both genotoxic and non-genotoxic pathways, which are not necessarily mutually exclusive. Most of the mechanistic studies have focused on either general genotoxicity or issues considered relevant to the mouse lung tumors, and there has been little research on mechanisms specific to lymphohematopoietic cancer in humans. Possible

modes of action for styrene-induced carcinogenicity involve (1) genotoxicity (relevant to all types of cancer), (2) cytotoxic effects of styrene metabolites in the mouse lung, and (3) immunosuppression (relevant to lymphohematopoietic cancer).

Genotoxicity

Most of the genetic damage associated with styrene exposure is thought to be due to styrene-7,8-oxide. The predominant DNA adducts formed as a result of styrene-7,8-oxide exposure occur at the N7, N², and O⁶ positions of guanine (these have been detected in cells); however, styrene-7,8-oxide adducts can also form at the N1, N3, and N⁶ positions of adenine, the N3, N⁴, and O² positions of cytosine, and the N3 position of thymine. N7-adducts are formed in the largest amounts but are the least persistent (i.e., they are either repaired or lost), whereas O⁶-adducts are formed in the smallest amounts but are the most persistent. Other than the N7-guanine and N3-adenine adducts, the styrene-7,8-oxide–DNA adducts listed above are considered promutagenic, because they can interfere with base pairing and lead to miscoding during DNA replication. The major styrene-7,8-oxide adduct at N7-guanine may also be promutagenic, because it can undergo spontaneous or glycosylase-mediated depurination, thus creating abasic sites that promote coding errors during DNA replication (Vodicka *et al.* 2006a). Styrene-7,8-oxide, without metabolic activation, is mutagenic in most *in vitro* systems, causing a variety of transition and transversion mutations (Bastlová and Podlutzky 1996). Both styrene and styrene-7,8-oxide caused cytogenetic effects (sister chromatid exchange, chromosomal aberrations, and micronucleus formation) in human lymphocytes or other mammalian cells *in vitro*. In mice and rats exposed to styrene *in vivo*, N7-guanine, O⁶-guanine, and N1-adenine adducts were detected in liver and lung cells (Pauwels *et al.* 1996, Boogaard *et al.* 2000b, Vodicka *et al.* 2001, 2006a,b). Most studies in mice also found single-strand DNA breaks following exposure to styrene-7,8-oxide or styrene (Wallis and Orsen 1983, Vaghef and Hellman 1998, Vodicka *et al.* 2001), and the cytogenetic effect reported most consistently was sister chromatid exchange (Conner *et al.* 1979, 1980, Sharief *et al.* 1986, Kligerman *et al.* 1992, 1993, Simula and Priestly 1992; reviewed by IARC 1994, 2002 and Scott and Preston 1994).

Styrene-7,8-oxide was measured in the blood of styrene-exposed workers, and several different styrene-7,8-oxide–based DNA adducts were detected in their lymphocytes. Styrene-7,8-oxide–DNA adducts identified in exposed workers include O⁶-guanine, N1-adenine, and N²-guanine. Styrene-7,8-oxide adducts were also detected in human volunteers exposed to styrene under conditions designed to eliminate or minimize non-enzymatic oxidation to styrene-7,8-oxide (Johanson *et al.* 2000). Adduct studies in workers showed that a DNA-reactive intermediate of styrene metabolism circulates in the blood of styrene-exposed humans (Vodicka *et al.* 2006a). The most consistent cytogenetic effects in styrene-exposed workers were single-strand DNA breaks and chromosomal aberrations (Anwar and Shamy 1995, Bonassi *et al.* 1996, Lazutka *et al.* 1999, Somorovská *et al.* 1999, reviewed by Cohen *et al.* 2002).

Lung Cytotoxicity in Mice

Cytotoxicity can cause regenerative hyperplasia, leading to the promotion of spontaneous or styrene-induced mutations and tumor formation. Styrene caused lung tumors and pulmonary toxicity in mice but did not cause lung tumors in rats (Cruzan *et al.* 1998, 2001). The induction of lung tumors in mice but not in rats has also been observed in studies of exposure to epoxides and other epoxide-forming chemicals, including the known human carcinogens vinyl chloride,

1,3-butadiene, and ethylene oxide (NTP 2004a,b; see the profiles for those substances).

Although several studies found no evidence of toxicity in the lungs of rats exposed to styrene (Cruzan *et al.* 1997, 1998, Green *et al.* 2001, Gamer *et al.* 2004), one study reported toxic effects on bronchiolar and alveolar type II cells in Sprague-Dawley rats exposed to styrene by inhalation or intraperitoneal injection (Coccini *et al.* 1997). Alveolar/bronchiolar hyperplasia from styrene exposure has been hypothesized to play a role in the development of lung tumors in mice. Effects of repeated styrene exposure in mice included focal crowding of bronchiolar cells, bronchiolar epithelial hyperplasia, and bronchiolar/alveolar hyperplasia (Cruzan *et al.* 2001). Interspecies differences in lung toxicity are proposed to result from differences in the extent of metabolism of styrene to ring-oxidized metabolites by Cyp2f in the Clara cells (Cruzan *et al.* 2002, 2009).

Indirect data supporting the role of Cyp2f in styrene-induced lung toxicity comes from short-term intraperitoneal-injection studies with wild-type and Cyp2e1 knock-out mice, which showed similar lung toxicity (Carlson 2004). Also, the cytotoxic effects of styrene and tumor formation were seen primarily in respiratory tissues that are high in Cyp2f isoforms, and Cyp2f inhibitors prevented cytotoxicity (Cruzan *et al.* 2002). Styrene-7,8-oxide, 4-vinylphenol, and 4-vinylphenol metabolites can be formed by Cyp2f2. Metabolites formed from ring oxidation, including 4-vinylphenol, occur at several-fold higher levels in mice than in rats (Boogaard *et al.* 2000a, Cruzan *et al.* 2002). Some data suggest that 4-vinylphenol is more toxic than styrene-7,8-oxide in mouse lung; however, the two metabolites were tested in separate experiments in two different mouse strains (Gadberry *et al.* 1996, Carlson 2002). Short-term toxicity studies of 4-vinylphenol in wild-type and Cyp2e1 knock-out mice and studies with CYP inhibitors suggest that metabolites of 4-vinylphenol are responsible for its lung and liver toxicity in mice (Carlson 2002, Vogie *et al.* 2004).

Immunosuppression

The mechanism for styrene-induced lymphohematopoietic cancer is not known. As discussed above, CYP2E1 is expressed in lymphocytes (Siest *et al.* 2008), and CYP2E1 protein and activity were detected in human hematopoietic stem cells (Kousalova *et al.* 2004), suggesting that styrene can be metabolized to styrene-7,8-oxide in the target tissues. Moreover, studies on genotoxicity and oxidative stress in styrene-exposed workers indicated that styrene causes DNA and chromosomal damage in peripheral blood lymphocytes. Immunosuppression has been proposed as a mechanism for solvent-induced lymphoma (Vineis *et al.* 2007). Styrene-exposed workers had decreased numbers of activated helper T-cell lymphocytes, suggesting that styrene exposure can cause immunosuppression; however, this study was limited in size, and the workers were exposed to other agents (Biró *et al.* 2002). In a review of studies in experimental animals and humans, Veraldi *et al.* (2006) concluded that there was “immediate” evidence for the immunotoxicity of styrene oxide, and that the main immunotoxic effect was immunosuppression.

Summary

Although styrene disposition differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard. Detection of styrene-7,8-oxide–DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action.

Properties

Styrene is an aromatic hydrocarbon that occurs as a colorless or yellowish viscous liquid with a sweet, floral odor (HSDB 2008). It has a flash point of 34°C (closed cup), a lower explosive limit of 0.9% to 1.1% v/v, an upper explosive limit of 6.1% to 6.8% v/v, and an auto-ignition temperature of 490°C. Styrene is highly flammable and easily ignited by heat, sparks, or flames, and its vapors may form explosive mixtures with air as a result of the formation of peroxides. Styrene may polymerize when contaminated by oxidizing agents or halides, or when heated, and it emits acrid fumes upon decomposition (SPA 2008, Akron 2010). Styrene usually is stabilized for safe storage, transport, and use by an inhibitor, commonly *p-tert*-butylcatechol (HSDB 2008). Other typical impurities are ethylbenzene, polymer content, aldehydes, peroxides (as H₂O₂), benzene, sulfur, and chlorides. Physical and chemical properties of styrene are listed in the following table.

Property	Information
Molecular weight	104.2
Specific gravity	0.906 at 20°C
Melting point	-31°C
Boiling point	145°C
Log <i>K</i> _{ow}	2.95
Water solubility	310 mg/L at 25°C
Vapor pressure	6.4 mm Hg at 25°C
Vapor density relative to air	3.6

Source: HSDB 2008.

Use

Styrene is an important industrial chemical, used in the synthesis and manufacture of polystyrene and hundreds of different copolymers, as well as numerous other industrial resins (Guest 1997). Styrene producers sell styrene monomer to companies that use styrene to make various compounds and resins. Fabricators then process the resins into a wide variety of products (Cohen *et al.* 2002). Roughly 99% of the industrial resins produced from styrene can be grouped into six major categories: polystyrene (50%), styrene-butadiene rubber (15%), unsaturated polyester resins (glass reinforced) (12%), styrene-butadiene latexes (11%), acrylonitrile-butadiene-styrene (10%), and styrene-acrylonitrile (1%). Another minor category of use is unsaturated polyester resins (not reinforced) (Luderer *et al.* 2005).

Polystyrene is used extensively in the manufacture of plastic packaging, thermal insulation in building construction and refrigeration equipment, and disposable cups and containers. Styrene polymers and copolymers are also increasingly used to produce various housewares, food containers, toys, electrical devices, automobile body parts, corrosion-resistant tanks and pipes, various construction items, carpet backings, house paints, computer printer cartridges, insulation products, wood-floor waxes and polishes, adhesives, putties, personal-care products, and other items, and they are used in paper processing (IARC 2002, Luderer *et al.* 2005, NLM 2008).

Styrene-butadiene rubber is the most widely used synthetic rubber in the world (ICIS 2008). Over 70% of styrene-butadiene rubber is consumed in the manufacture of tires and tire products; however, non-tire uses are growing, with applications including conveyor belts, gaskets, hoses, floor tiles, footwear, and adhesives.

Another major use of styrene is as a cross-linking agent in polyester resins used in gel-coating and laminating operations in the production of glass-fiber-reinforced plastic products such as boats, bathtubs, shower stalls, tanks, and drums (Miller *et al.* 1994, EPA 1997). The resins generally contain between 30% and 50% styrene by weight (EPA 1997).

Production

There are two commercially viable methods of producing styrene (ATSDR 1992, HSDB 2008). The most common process, which accounts for over 90% of total world styrene production, involves catalytic dehydrogenation of ethylbenzene. The second process involves oxidation of ethylbenzene to its peroxide, which is then reacted with propylene to produce propylene oxide and α -methylphenyl carbinol. The carbinol is then dehydrated to produce styrene. U.S. production of styrene has risen fairly steadily since 1960. Between 1960 and 2006, estimated production ranged from a low of 1,740 million pounds in 1960 to a high of 11,897 million pounds in 2000. In 2006, eight U.S. manufacturers produced an estimated 11,387 million pounds of styrene; the three largest producers accounted for 54% of production. U.S. consumption of styrene in 2006 was 9,600 million pounds, over 99% of which was consumed in the production of polymers and copolymers (Berthiaume and Ring 2006). U.S. imports and exports of styrene increased steadily from 1975 through 2007, from 7 million pounds to 1,475 million pounds for imports and from 574 million pounds to 4,200 million pounds for exports (Berthiaume and Ring 2006, USITC 2008a,b).

Exposure

Exposure to styrene can occur in both occupational and non-occupational settings. However, workers in certain occupations potentially are exposed to much higher levels of styrene than the general population. The greatest source of exposure for the general population is cigarette smoking, and daily styrene intake by the nonsmoking population is expected to be orders of magnitude lower than daily intakes for workers in occupations with high styrene exposure levels (Cohen *et al.* 2002, IARC 2002).

Exposure of the General Population

Styrene exposure to the general population can occur through environmental contamination. For the non-smoking general population, inhalation of indoor air and ingestion of food resulted in the highest daily styrene intakes (IARC 2002). Styrene has been measured in outdoor air, but higher levels generally are found in indoor air, drinking water, groundwater, surface water, soil, and food. Styrene can be emitted to the air from industrial production and use of styrene and styrene-based polymers and copolymers, motor-vehicle emissions and other combustion processes, offgassing of building materials and consumer products, and cigarette smoking (ATSDR 2010, IARC 1994). Numerous spills containing styrene have been reported to the National Response Center since 1990, and these spills have the potential to contaminate air, water, soil, and food supplies (NRC 2008). Uptake of styrene by biological organisms is expected to be low; however, styrene has been detected in fish and other aquatic organisms (Howard 1989, ECB 2002, HSDB 2008).

Food can contribute to styrene exposure (Lickly *et al.* 1995a, Tang *et al.* 2000, Cohen *et al.* 2002, Holmes *et al.* 2005). Styrene has been detected in a wide range of foods and beverages, with the highest measured levels occurring in unprocessed, raw cinnamon, possibly resulting from the natural degradation of cinnamic acid derivatives (IARC 1994). Styrene also occurs at very low concentrations in many agricultural food products; however, it is not known whether the styrene is produced endogenously or results from environmental contamination (Tang *et al.* 2000). The presence of styrene in packaged foods is due primarily to leaching of monomer from polystyrene containers (Howard 1989, ATSDR 2010). The rate of migration of styrene monomer from polystyrene containers is determined mainly by the lipophilicity of the food, surface area of the container per volume of

food, duration of contact, and food temperature (ATSDR 2010, Lickly *et al.* 1995b, ECB 2002, Choi *et al.* 2005).

In a study comparing styrene intake from various sources, estimated daily intake for adults was lowest from polluted drinking water and highest from cigarette smoke, polluted urban air, and indoor air (Fishbein 1992). Estimated daily styrene intake for the Canadian general population from sources other than smoking was less than 0.8 µg/kg of body weight for children and less than 0.4 µg/kg for adults, but estimated daily intake for cigarette smokers was as high as 3.5 µg/kg (CEPA 1993). While this study demonstrated that inhalation of both indoor and outdoor air and ingestion of food are important sources of exposure for nonsmokers, it also estimated that exposure from smoking cigarettes was roughly 10 times that from all other routes (indoor and outdoor air, drinking water, soil, and food) combined. Other studies estimated that styrene exposure of smokers was six times that of nonsmokers (Cohen *et al.* 2002) and that up to 15% of nonsmokers' styrene exposure could be attributed to environmental tobacco smoke (Miller *et al.* 1998).

In a 1982 study by the U.S. Environmental Protection Agency, styrene was detected in all of eight human-breast milk samples from women in four U.S. cities and in all of an unspecified number of wet adipose tissue samples (Howard 1989). Styrene also was detected in the general population at mean concentrations of 0.4 µg/L in blood and 0.7 to 1.6 µg/m³ in exhaled breath (ATSDR 2010). Blood styrene levels were assessed in the Priority Toxicant Reference Range Study conducted as part of the Centers for Disease Control and Prevention's Third National Health and Nutrition Examination Survey. Of 624 samples, 78 (12.5%) contained no detectable styrene, and 546 contained styrene at concentrations ranging from 0.019 to 4.006 µg/L; the mean concentration for all 624 samples was 0.07 µg/L, the median was 0.04 µg/L, and the 95th percentile value was 0.18 µg/L (Ashley *et al.* 1994, Sexton *et al.* 2005).

Occupational Exposure

Workers can be exposed to styrene during production of styrene monomer, polystyrene and various styrene copolymers, glass-fiber-reinforced plastics, and styrene-butadiene rubber; exposure can also occur in other miscellaneous occupations (ATSDR 2010, IARC 2002).

The highest levels of occupational exposure to styrene occur in the fabrication of products such as boats, car and truck parts, tanks, bathtubs, and shower stalls from glass-fiber-reinforced polyester composite plastics (IARC 2002). Historically, the highest styrene exposure levels for reinforced-plastics workers were in the range of several hundred parts per million; however, estimated exposure levels have decreased by a factor of 10 over the past several decades as a result of improved work practices and products (Kolstad *et al.* 2005). In general, the average exposure levels reported since the 1980s have been less than 100 ppm. In 2006, the U.S. Bureau of Labor Statistics estimated that 32,510 workers were employed as Fiberglass Laminators and Fabricators (defined as "laminated layers of fiberglass on molds to form boat decks and hulls, bodies for golf carts, automobiles, or other products"). Ship and Boat Building was the largest subcategory in this Standard Occupational Classification segment, with 12,910 employees (BLS 2007). Workers in the reinforced-plastics industry are potentially exposed to styrene-7,8-oxide, as well as styrene, but at levels 2 to 3 orders of magnitude lower than styrene (Serdar *et al.* 2006).

Styrene exposure levels are generally lower in the styrene-butadiene rubber and the styrene monomer and polymer industries than in the reinforced-plastics industry; however, significant exposure of workers still can occur. Reported mean exposure levels for these industries generally have been less than 20 ppm. No data were found on the numbers of employees in these industries. As in the

reinforced-plastics industry, styrene exposure levels in these industries have declined over the past several decades (Macaluso *et al.* 1996, IARC 2002).

Low levels of styrene (usually in the low parts-per-billion range) have been reported in a variety of other occupational settings, including nuclear power plants, photocopy centers, a petrochemical complex, printing plants, wood surface-coating operations, tollbooths, and a waste incinerator, and during the production of PVC film (Kim *et al.* 2003, Bakoğlu *et al.* 2004, Leung *et al.* 2005, Sapkota *et al.* 2005, Thorud *et al.* 2005, Chan *et al.* 2006, Hsieh *et al.* 2006, Lee *et al.* 2006). Levels in the low parts-per-million range were measured in a sculpture class where polyester resins were used, during the production of buttons, and during firefighting. Higher levels were seen during the production or use of paints and putties (exceeding 20 ppm), for taxidermists (up to 70 ppm), and during the manufacture of cooking ware (up to 186 ppm) (IARC 2002).

Regulations

Coast Guard, Department of Homeland Security

46 CFR 150 and 151 detail procedures for shipping styrene monomer and for shipping styrene monomer and various styrene co-polymers with incompatible mixtures.

Department of Transportation (DOT)

Styrene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of styrene is subject to certain provisions for the control of volatile organic compound emissions.

Clean Water Act

Designated a hazardous substance.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.1 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.1 mg/L.

The food additive poly(2-vinylpyridine-co-styrene) may be safely used as a nutrient protectant in feed for beef cattle and dairy cattle and replacement dairy heifers, with residual styrene levels not to exceed 200 ppb.

Polystyrene basic polymers used as components of articles intended for use in contact with food shall contain not more than 1% by weight of total residual styrene monomer (0.5% by weight for certain fatty foods).

Rubber-modified polystyrene basic polymers used as components of articles intended for use in contact with food shall contain not more than 0.5% by weight of total residual styrene monomer.

Styrene-maleic anhydride co-polymers may be used as articles or as components of articles intended for use in contact with food provided that conditions are met, including residual styrene monomer levels not exceeding 0.3% by weight.

Styrene-acrylic co-polymers may be used as components of the food-contact surface of paper and paperboard provided that certain conditions are met, including residual styrene monomer levels not exceeding 0.1% by weight.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Acceptable peak exposure = 600 ppm (5-min maximum peak in any 3 h).

Ceiling concentration = 200 ppm.

Permissible exposure limit (PEL) = 100 ppm.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 20 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 40 ppm.

Biological exposure indices: Mandelic acid plus phenylglyoxylic acid in urine, end of shift = 400 mg/g of creatinine; styrene in venous blood, end of shift = 0.2 mg/L.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 700 ppm.

Short-term exposure limit (STEL) = 100 ppm.

Recommended exposure limit (REL) = 50 ppm.

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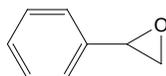
Styrene-7,8-oxide

CAS No. 96-09-3

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as 1,2-epoxyethylbenzene



Carcinogenicity

Styrene-7,8-oxide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to styrene-7,8-oxide caused tumors in two rodent species and at two different tissue sites. Styrene-7,8-oxide (styrene oxide) administered by stomach tube caused cancer of the forestomach (squamous-cell carcinoma) in both sexes of mice (one strain) and rats (three strains) (IARC 1994). It also caused liver tumors (hepatocellular tumors) in male mice (Lijinsky 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to styrene-7,8-oxide.

Studies on Mechanisms of Carcinogenesis

Styrene oxide given orally to rabbits, rats, and mice is absorbed and broken down rapidly in the acid environment of the stomach and excreted almost completely in the urine. Styrene oxide can be metabolized by epoxide hydrolase to form the glycol or by glutathione S-transferase to glutathione conjugates. Styrene glycol is further metabolized to mandelic, phenylglyoxylic, and hippuric acids, which are excreted in urine (IARC 1976, 1994). Workers exposed to styrene oxide vapors excreted large amounts of mandelic acid and phenylglyoxylic acid in their urine. (Fustinoni *et al.* 1998).

Styrene oxide caused mutations in bacteria, yeast, insects, and cultured mammalian cells, including mutations at the *hprt* locus in Chinese hamster V79 cells and human T lymphocytes. It caused chro-

mosomal aberrations or sister chromatid exchange in Chinese hamster V79 cells, Chinese hamster ovary cells, mouse bone marrow cells *in vivo*, and cultured human lymphocytes. It also caused DNA strand breaks in cultured primary animal hepatocytes, human embryonal cells, human lymphocytes, mouse lymphocytes, and mouse liver and kidney cells (IARC 1994).

Styrene oxide-DNA adducts were observed at low levels in the forestomachs of male rats given styrene oxide orally (Lutz *et al.* 1993). DNA adducts that formed at very low levels in the livers of mice administered styrene orally were attributed to styrene oxide, as styrene was presumed to have been almost completely metabolized to styrene oxide (Cantoreggi and Lutz 1993). A study of workers in a boat-making facility where styrene concentrations ranged from 1 to 235 mg/m³ (mean = 65.6 mg/m³, or 13.3 ppm) found elevated levels of styrene oxide-DNA adducts in mononuclear cells (Huff 1984, McConnell and Swenberg 1993). Styrene oxide-DNA and styrene oxide-albumin adducts were found in the blood of plastics workers exposed to styrene oxide (Fustinoni *et al.* 1998). Styrene oxide-DNA adducts in rodents and humans appear to be similar. There is no evidence to suggest that mechanisms by which styrene oxide causes genotoxic effects and tumors in experimental animals would not also operate in humans.

Properties

Styrene-7,8-oxide is an epoxide of styrene that exists at room temperature as a colorless to pale yellow liquid with a pleasant sweet odor. It is soluble in alcohol, ether, benzene, acetone, methanol, carbon tetrachloride, and heptane, and miscible with most other organic solvents. It is only slightly soluble in water. Styrene-7,8-oxide polymerizes exothermally and reacts vigorously in the presence of catalysts with compounds with available hydrogen ions (IARC 1994). Physical and chemical properties of styrene-7,8-oxide are listed in the following table.

Property	Information
Molecular weight	120.2 ^a
Specific gravity	1.0523 at 16°C/4°C ^a
Melting point	-35.6°C ^a
Boiling point	194.1°C ^a
Log K _{ow}	1.61 ^a
Water solubility	3.000 g/L at 20°C ^b
Vapor pressure	0.3 mm Hg at 20°C ^a
Vapor density relative to air	4.3 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Styrene oxide is used as a chemical intermediate in the production of styrene glycol and its derivatives, cosmetics, surface coatings, and agricultural and biological chemicals. It also is used as a reactive diluent for epoxy resins and in cross-linked polyesters and polyurethanes. Styrene oxide has been used as a raw material for the production of 2-phenylethanol (oil of roses) used in perfumes and in the treatment of fibers and textiles. Small quantities are used to improve the stability of hydraulic fluids, chlorinated cleaning compositions, petroleum distillates, dielectric fluids, and acid-sensitive polymers and copolymers (IARC 1994, HSDB 2009).

Production

Styrene oxide was listed by the U.S. Environmental Protection Agency as a high-production-volume chemical in 1990, indicating that annual production exceeded 1 million pounds (EPA 2006). In 2009, one U.S. manufacturer of styrene oxide was identified (HSDB 2009). Reports filed under EPA's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of styrene oxide

totalled over 1 million to 10 million pounds in 1990 and 10,000 to 500,000 pounds in 1986, 1994, 1998, and 2002 (EPA 2004).

Exposure

The general population may be exposed to styrene oxide by contact with contaminated air or water; however, according to EPA's Toxics Release Inventory, annual environmental releases of styrene oxide from industrial facilities were less than 100 lb until 2006. In 2006 and 2007, larger quantities (246 lb and 380 lb, respectively) were sent to off-site hazardous-waste landfills (TRI 2009). No quantitative exposure data were found.

In a study in the United Kingdom, various plastics and resins were analyzed to determine whether styrene oxide could migrate to food. Styrene oxide was found in items that came into contact with food, including 9 base resins and 16 samples of polystyrene articles. Concentrations of styrene oxide in typical polystyrene materials were low, ranging from undetectable (< 0.5 mg/kg) to 3 mg/kg. Assuming that styrene oxide migrates in the same pattern as the styrene monomer, estimated concentrations in food resulting from migration ranged from 0.002 to 0.15 µg/kg (Philo *et al.* 1997).

Occupational exposure to styrene oxide occurs most often in the fabricated rubber products, paints, and allied products industry (HSDB 2009). Occupational exposure to styrene oxide is primarily indirect via exposure to styrene. Styrene oxide can form in air at low levels (< 1 mg/m³, or < 203 ppb) when styrene reacts with oxygen or hydroperoxides (used to initiate the curing of reinforced plastics) (Yeowell-O'Connell *et al.* 1997). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 333,212 workers, including 86,902 women, potentially were exposed to styrene, and that 458 workers potentially were exposed to styrene oxide (NIOSH 1990).

In personal exposure air samples for 19 workers at a U.S. boat manufacturing company who were heavily exposed to styrene by inhalation (at a mean concentration of 64 mg/m³), the average concentration of styrene oxide was 0.14 mg/m³ (28.5 ppb) (IARC 1994). Nylander-French *et al.* (1999) studied levels of styrene oxide exposure and factors contributing to exposure in workers who manufactured reinforced plastics. From laboratory experiments, they hypothesized that styrene oxide formed by (1) breakdown of polymeric styrene peroxide radicals resulting from the copolymerization of styrene and oxygen, (2) epoxidation of the styrene monomer, or (3) reaction of styrene with volatile organic peroxides used in curing reinforced plastics. However, no measurements in manufacturing plants have confirmed these hypotheses. Among workers, styrene oxide exposure increased with increasing styrene exposure, but this correlation was statistically significant only among hand laminators, who were exposed to the highest levels of styrene and styrene oxide. Resin use also was an important factor in predicting styrene oxide exposure, regardless of the quantity of resin used. It was concluded that styrene oxide exposure was affected by factors other than styrene exposure.

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

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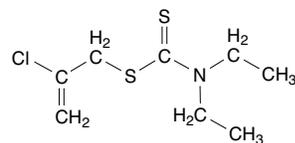
Sulfallate

CAS No. 95-06-7

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as *N,N*-diethyldithiocarbamic acid 2-chloroallyl ester or 2-chloroallyl diethyl(dithiocarbamate)



Carcinogenicity

Sulfallate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to sulfallate caused tumors in two rodent species and at several different tissue sites. Dietary administration of sulfallate

caused cancer of the mammary gland (adenocarcinoma) in female rats and mice, cancer of the forestomach (squamous-cell carcinoma) in male rats, and benign lung tumors (alveolar/bronchiolar adenoma) in male mice (IARC 1983, NCI 1980). Since sulfallate was listed in the *Third Annual Report on Carcinogens*, an additional study in mice has been identified. In male and female strain A mice (a strain with a high spontaneous incidence of lung cancer), intraperitoneal injection of sulfallate increased the number of lung tumors per animal (Maronpot *et al.* 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to sulfallate.

Properties

Sulfallate is a chlorinated dithiocarbamate derivative that exists as an amber oil at room temperature (NCI 1980, HSDB 2009). It is very slightly soluble in water and soluble in acetone, benzene, chloroform, ethyl acetate, ethyl alcohol, kerosene, and most other organic solvents. It is hydrolyzed by alkalis (IARC 1983). Physical and chemical properties of sulfallate are listed in the following table.

Property	Information
Molecular weight	223.8 ^a
Specific gravity	1.088 at 25°C ^a
Boiling point	128°C to 130°C ^a
Log K_{ow}	3.15 ^b
Water solubility	0.100 g/L at 25°C ^a
Vapor pressure	2.2×10^{-3} mm Hg at 20°C ^a
Dissociation constant (pK_a)	13.30 ^c

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009.

Use

Sulfallate was first introduced as a herbicide in 1954 (IARC 1983). Its primary use in the United States was as a pre-emergent selective herbicide to control certain annual grasses and broadleaf weeds around vegetable and fruit crops (HSDB 2009). Sulfallate was also used to control weeds among shrubbery and ornamental plants. All sulfallate products were discontinued by the manufacturer in the early 1990s (EPA 1998, HSDB 2009).

Production

Commercial production of sulfallate in the United States was first reported in 1955 (IARC 1983). About 100,000 lb of sulfallate was used in the United States in 1975 and 1978 (HSDB 2009). No data on current U.S. production, imports, or exports of sulfallate were found. In 2009, sulfallate was available from eight suppliers worldwide, including seven U.S. suppliers (ChemSources 2009).

Exposure

Because sulfallate is no longer used in the United States, the potential for exposure is low. In the past, the general population may have been exposed to sulfallate through ingestion of residues in food crops, and rural residents may have been exposed through inhalation or dermal contact after spraying applications. Sulfallate was identified in vegetables in the 1978 to 1982 and 1988 to 1989 pesticide monitoring programs conducted by the U.S. Food and Drug Administration (HSDB 2009).

If released to air, sulfallate will remain in the vapor phase and react with photochemically produced hydroxyl radicals, with a half-life of 4 hours (HSDB 2009). If released to water, sulfallate will adsorb to sediment and suspended particles or will volatilize. If released to soil, it will be moderately mobile and will remain in surface soil for about

six weeks. If sulfallate remains in surface soil, it may be carried with eroding soil from agricultural land into surface water.

The potential for occupational exposure through inhalation and dermal contact existed during the manufacture, formulation, and application of sulfallate (HSDB 2009). The potential for exposure was greatest for agricultural workers during application.

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

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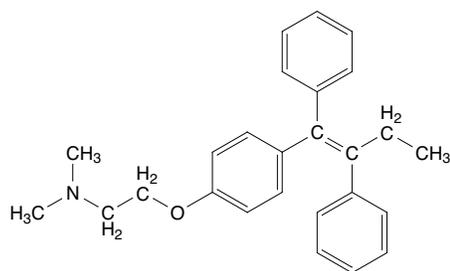
Tamoxifen

CAS No. 10540-29-1

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Also known as (Z)-2-[4-(1,2-diphenylbut-1-enyl)phenoxy]-N,N-dimethyl-ethanamine



Carcinogenicity

Tamoxifen is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Data from epidemiological studies and clinical trials indicate a causal relationship between exposure to tamoxifen and cancer of the uterus (endometrial type). However, there also is conclusive evidence that tamoxifen therapy reduces the risk of contralateral breast cancer in women with a previous diagnosis of breast cancer and may prevent or delay the occurrence of breast cancer in women at increased risk for this disease (IARC 1996). By the mid 1990s, the potential effect of tamoxifen in increasing the risk of endometrial cancer had been

reported in one adequate cohort study, four adequate case-control studies, and fourteen randomized clinical trials.

The cohort study (Curtis *et al.* 1996) examined the effect of tamoxifen on the risk of endometrial cancer in 87,323 women with breast cancer reported to the National Cancer Institute's Surveillance, Epidemiology, and End Results program and found a significant excess of endometrial cancer among women who had received tamoxifen therapy. Two of the four case-control studies (van Leeuwen *et al.* 1994, Sasco *et al.* 1996) found statistically nonsignificant increases in the risk of endometrial cancer; however, among women treated with tamoxifen, risk increased significantly with increasing duration of therapy and cumulative dose in one of these studies (van Leeuwen *et al.* 1994). The third case-control study, conducted in the United States, found no increased risk; however, the duration of tamoxifen use was shorter than in the other studies (Cook *et al.* 1995). The fourth case-control study found an increased risk of endometrial cancer with tamoxifen use; however, the effects of potentially confounding factors could not be ruled out (Hardell 1988).

The two largest randomized clinical trials found a strong, significant association between risk of endometrial cancer and use of tamoxifen (Fisher *et al.* 1994, Rutqvist *et al.* 1995). In the 12 smaller trials, the incidence of endometrial cancer was not significantly increased; however, when the results of these 12 studies were combined, 29 cases of endometrial cancer were reported in tamoxifen-treated individuals, compared with 14 in the control group (IARC 1996). In 32 case studies, 102 cases of endometrial cancer were reported in women who had received tamoxifen for breast cancer. One case series reported significantly more high-grade endometrial tumors in tamoxifen-treated breast-cancer patients than in patients who had not received tamoxifen (Magriples *et al.* 1993); this difference, however, was not observed in six other studies (IARC 1996).

In a review, MacMahon (1997) concluded that the published results suggested a causal association between tamoxifen use and endometrial cancer but were not conclusive, because of confounding factors such as prior hysterectomy or hormone replacement therapy. The International Agency for Research on Cancer examined the same potentially confounding factors but considered them unlikely to have had a major effect on the reported relative risks; IARC therefore concluded that several of the studies cited supported a positive association between tamoxifen use and endometrial cancer (IARC 1996).

Cancer Studies in Experimental Animals

Uterine abnormalities, including endometrial cancer (carcinoma), have been reported in experimental animals exposed to tamoxifen. Rats receiving tamoxifen daily by stomach tube for 20 to 52 weeks developed squamous-cell metaplasia, dysplasia, and carcinoma of the uterus; no comparable lesions were observed in controls (Mantyla *et al.* 1996). In newborn mice of both sexes, exposure to tamoxifen on days 1 to 5 of life significantly increased the incidence of reproductive-tract abnormalities, including uterine cancer and seminal-vesicle tumors (Newbold *et al.* 1996, 1997). Tamoxifen administered orally to mice for three months caused benign ovarian and testicular tumors. In eight studies in rats with various exposure durations, tamoxifen caused precancerous liver lesions and benign or malignant liver tumors. One study in rats reported a decreased incidence of tumors in hormone-dependent tissues; however, reduced weight gain may have been a contributing factor. In intact and ovariectomized mice given tamoxifen by subcutaneous injection, development of mammary-gland tumors was inhibited (IARC 1996).

Studies on Mechanisms of Carcinogenesis

Several studies found that women receiving estrogen-replacement therapy unopposed by progesterone had highly elevated risks of endo-

metrial cancer (IARC 1979, 1999). For this reason, conjugated estrogens are classified as *known to be human carcinogens* (see Estrogens, Steroidal). Tamoxifen acts as an anti-estrogen in the breast (and is therefore used to treat breast cancer), but acts as an estrogen agonist in the uterus. Therefore, tamoxifen will likely affect the uterus in the same way as conjugated estrogens. The available data strongly indicate that endometrial cancer following exposure to estrogen is caused by estrogen-receptor-mediated responses.

In experimental animals and *in vitro*, tamoxifen readily forms DNA adducts in several tissues and types of cells. Either these adducts or the estrogenic activity of tamoxifen could be responsible for liver cancer observed in rats exposed to tamoxifen. DNA adducts generally have not been detected in human tissue samples; however, low levels of DNA adducts were observed in leukocytes and endometrial tissue from breast-cancer patients receiving tamoxifen (Hemminki *et al.* 1996, 1997). Although tamoxifen did not cause mutations in bacteria, it induced micronucleus formation in human cells *in vitro* (Otto *et al.* 1996). *In vivo*, it increased aneuploidy and chromosomal aberrations in the livers of female Sprague-Dawley rats (Sargent *et al.* 1996). The available data indicate that the carcinogenicity of tamoxifen in humans is due to estrogen-receptor-mediated mechanisms. Genotoxic mechanisms may also be involved in human cancer, but the available data suggest that genotoxic effects are smaller in humans than in rodents.

Tamoxifen has been tested in tumor initiation-promotion studies (IARC 1996). In rats, it promoted the development of *N*-nitrosodiethylamine-induced liver tumors in several studies and kidney tumors in one study. In several other studies in rats, tamoxifen inhibited the development of 7,12-dimethyl[*a*]benzanthracene-induced mammary-gland tumors. In mice, tamoxifen inhibited the development of 3-methylcholanthrene-induced cervical cancer and virus-induced leukemia. In two studies in hamsters, it inhibited the development of kidney and liver tumors induced by 17 β -estradiol.

Properties

Tamoxifen is a triphenylethylene compound that is a white, odorless crystal at room temperature (HSDB 2009). It is practically insoluble in water, but soluble in ethanol, methanol, and acetone. Physical and chemical properties of tamoxifen are listed in the following table.

Property	Information
Molecular weight	371.5 ^a
Melting point	96°C to 98°C ^a
Log K_{ow}	6.3 ^a
Dissociation constant (p <i>K_b</i>)	5.31 (p <i>K_b</i>) ^b

Sources: ^aHSDB 2009, ^bAkron 2009.

Use

Tamoxifen was approved for pharmaceutical use in the United States in 1977. It is registered for use in more than 90 countries. Tamoxifen has proven to be a successful palliative therapy for advanced breast cancer, yielding response rates similar to those seen with other endocrine treatments but with fewer side effects. It is commonly used as a primary therapy for breast cancer in elderly women who are considered poor candidates for surgery. Tamoxifen has been the adjuvant therapy of choice for postmenopausal, node-positive, and estrogen- or progesterone-receptor-positive women since the mid 1980s, and for postmenopausal, node-negative, and estrogen- or progesterone-receptor-positive women since the early 1990s. It is also being used to treat breast cancer in node-negative and receptor-positive premenopausal women. A high proportion (40% to 60%) of all women who undergo potentially curative surgery for breast cancer now receive adjuvant tamoxifen therapy for two to five years (IARC 1996).

Tamoxifen is also used to reduce the risk of breast cancer in women who are at high risk for developing the disease (HHS 1998). Tamoxifen has been tested as a possible treatment for other types of cancer, including melanoma and cancer of the liver (hepatocellular carcinoma), stomach, kidney (renal-cell carcinoma), pancreas (adenocarcinoma), cervix of the uterus, and ovary; however, it is not widely used for these purposes (IARC 1996). Worldwide use of tamoxifen from its market introduction through July 2001 was estimated at more than 12 million patient-years (Wickerham *et al.* 2002).

Production

Worldwide production of tamoxifen citrate (the salt used as the active ingredient in most drug products) increased steadily in the 1990s, from 7 metric tons (15,400 lb) in 1989 to 8.5 metric tons (18,700 lb) in 1991, 10.1 metric tons (22,300 lb) in 1993, and 10.3 metric tons (22,700 lb) in 1995 (IARC 1996). In 2009, one company (in Europe) produced tamoxifen, and twelve companies worldwide produced tamoxifen citrate (none in the United States) (SRI 2009); tamoxifen was available from seven U.S. suppliers, and tamoxifen citrate from fourteen U.S. suppliers (ChemSources 2009). In 2009, five U.S. pharmaceutical companies produced 10 drug products approved by the U.S. Food and Drug Administration that contained tamoxifen citrate as the active ingredient (FDA 2009).

Exposure

Exposure to tamoxifen may occur by ingestion or by inhalation of dust (ScienceLab 2008). Tamoxifen is available in 10- and 20-mg oral tablets, taken in the United States at a typical dose of 20 mg per day for one to two years. Daily doses in other countries may be as high as 30 to 40 mg. Tamoxifen citrate is available in 15.2-, 30.4-, and 45.6-mg tablets that contain 10, 20, and 30 mg of tamoxifen, respectively (FDA 2009). Most patients with metastatic breast cancer (men and women) are treated with tamoxifen at some point in their therapy (IARC 1996). In 2002, tamoxifen was the world's most commonly prescribed breast-cancer drug; one pharmaceutical company reported sales totaling \$480 million, down 21% from \$618 million in 2001. By 2005, annual sales had declined to \$114 million (AstraZeneca 2003, 2006). Sales of generic forms of tamoxifen totaled \$420 million for about 3,400,000 prescriptions in 2002, declining to \$50 million for 1,670,000 prescriptions in 2007 (DrugTopics 2003a,b, 2008a,b).

Occupational exposure to tamoxifen may occur during its production, formulation, packaging, and administration. According to the National Occupational Exposure Survey (conducted from 1981 to 1983), 339 workers potentially were exposed to tamoxifen, and 2,077 workers potentially were exposed to tamoxifen citrate (NIOSH 1990).

Regulations

Consumer Product Safety Commission (CPSC)

Orally administered prescription drugs for human use require child-resistant packaging.

Food and Drug Administration (FDA)

Tamoxifen is regulated as a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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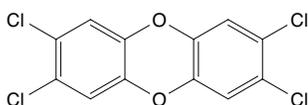
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

CAS No. 1746-01-6

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as dioxin, TCDD, or 2,3,7,8-TCDD



Carcinogenicity

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, both epidemiological and on the mechanism of carcinogenesis. TCDD was first listed in the *Second Annual Report on Carcinogens* as *reasonably anticipated to be a human carcinogen*. Subsequently, a number of studies were published that examined cancer in human populations exposed to TCDD occupationally or through industrial accidents. A concerted research effort examined the molecular and cellular events that occur in tissues of humans and animals exposed to TCDD. Based on the new information, the listing was revised to *known to be a human carcinogen* in the January 2001 addendum to the *Ninth Report on Carcinogens*.

Cancer Studies in Humans

Epidemiological studies of four industrial cohorts with high exposure to TCDD, in Germany (two separate studies), the Netherlands, and the United States, found increases in overall mortality from cancer. An exposure-response relationship was observed in the largest and most heavily exposed German cohort. The International Agency for Research on Cancer evaluated data from the most heavily exposed subcohorts in studies published through 1996 and found that the risks of all cancer combined, lung cancer, and non-Hodgkin's lymphoma were significantly increased. Increased risks of certain types of cancer also were found in an updated examination of the population exposed to TCDD during a 1976 industrial accident in Seveso, Italy (IARC 1997). After TCDD was listed in the *Ninth Report on Carcinogens*, IARC concluded that there was sufficient evidence of the carcinogenicity of TCDD in humans based on increased risk of all cancer combined (Baan *et al.* 2009).

Studies on Mechanisms of Carcinogenesis

There is scientific consensus for a common mode of action of TCDD and other chlorinated dibenzodioxins, dibenzofurans, and planar polychlorinated biphenyls (PCBs). In humans and rodents, this mode of action involves events that stem from the initial binding of TCDD

to the aryl or aromatic hydrocarbon (Ah) receptor. The Ah receptor is a ubiquitous protein in the cells of vertebrates (including rodents and humans), which acts as a signal transducer and activator for gene transcription. Of all the chlorinated dioxins and furans, TCDD has the highest affinity for both rodent and human forms of the Ah receptor. Through activation of the Ah receptor, TCDD causes a wide spectrum of biological responses considered important to the carcinogenic process, including changes in gene expression, altered metabolism, altered cell growth and differentiation, and disruption of steroid-hormone and growth-factor signal-transduction pathways. Similar Ah-receptor-mediated responses have been observed in humans and rodents at similar body burdens or tissue concentrations of TCDD (DeVito *et al.* 1995). The scientific consensus is that binding to the Ah receptor is a necessary, but not sufficient, step in eliciting these TCDD-induced responses, including cancer.

One major difference between humans and rodents has been noted: TCDD has a half-life of 5.8 to 11.3 years in humans (Olson 1994), compared with generally 10 to 30 days in rodents (IARC 1997). Thus, TCDD accumulates in human tissue at a higher rate than in most experimental animals as a result of chronic low-level exposure. This increased accumulation suggests that TCDD-induced responses would occur in humans following prolonged exposure at lower daily intakes than would be required to elicit similar responses in experimental animals.

TCDD is not believed to be mutagenic. *In vivo* and *in vitro* genotoxicity studies of TCDD in human and animal cells have given inconsistent findings, and findings of chromosomal aberrations in humans exposed *in vivo* to TCDD are equivocal (IARC 1997).

Cancer Studies in Experimental Animals

Since 1977, many independent studies have all found TCDD to be carcinogenic in experimental animals. TCDD caused tumors in various strains of rats, mice, and hamsters, in both sexes, at numerous tissues sites, and by several different routes of exposure, including oral (dietary or by stomach tube), dermal, and intraperitoneal. Tissue sites at which cancer occurred included the liver, thyroid gland, lymphatic system, respiratory tract, adrenal cortex of the kidney, hard palate, nasal turbinates, tongue, and skin (Huff *et al.* 1994). TCDD caused cancer in a dose-dependent fashion and was also a potent promoter of liver and skin cancer in initiation-promotion studies. In addition, a compelling body of evidence indicates that the biochemical and toxicological responses to TCDD in experimental animals and humans have a similar mechanism of action.

Properties

TCDD is the index constituent for the class of compounds called dioxins. It occurs as colorless-to-white needles at room temperature. It is insoluble in water and very slightly soluble in *o*-dichlorobenzene, chlorobenzene, benzene, chloroform, acetone, *n*-octanol, methanol, and lard oil. Physical and chemical properties of TCDD are listed in the following table.

Property	Information
Molecular weight	322.0
Melting point	305°C to 306°C
Log K_{ow}	6.8
Water solubility	2×10^{-7} g/L at 25°C
Vapor pressure	1.50×10^{-9} mm Hg at 25°C

Source: HSDB 2009.

Use

TCDD has no known commercial applications, but it is used as a research chemical. It was tested, but never used commercially, as

a flameproofing agent and as a pesticide against insects and wood-destroying fungi (ATSDR 1998, HSDB 2009). TCDD occurred as a contaminant in chlorophenoxy herbicides, including 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), that were widely used in the 1960s and 1970s to control weeds (including controlling weeds on pastureland and food crops) and as a defoliant during the Vietnam War (see Production and Exposure, below).

Production

TCDD is not currently produced commercially in the United States, but it is synthesized on a laboratory scale. In 2009, TCDD was available from at least six U.S. suppliers (ChemSources 2009). TCDD is not imported into the United States (ATSDR 1998). Polychlorinated dibenzo-*p*-dioxins (CDDs), including TCDD, are inadvertently produced by paper and pulp bleaching (Silkworth and Brown 1996), by incineration of municipal, toxic, and hospital wastes, in PCB-filled electrical transformer fires, in smelters, and during production of chlorophenoxy herbicides (Schechter 1994, IARC 1997, Schechter *et al.* 1997b). The greatest unintentional production of CDDs occurs from waste incineration, metal production, and fossil-fuel and wood combustion (ATSDR 1998).

Because TCDD is a by-product of the manufacture of polychlorinated phenols, it has been detected in commercial samples of 2,4,5-trichlorophenol (2,4,5-TCP), pentachlorophenol (a wood preservative), and the herbicide 2,4,5-T. Before 1965, commercial 2,4,5-T contained TCDD at concentrations of up to 30 ppm or more. By the mid 1980s, however, commercial 2,4,5-T contained no more than 0.01 ppm TCDD. Since 1971, regulatory agencies in a number of countries worldwide have enforced a maximum TCDD concentration of 0.1 ppm in 2,4,5-T. Millions of gallons of Agent Orange (a 50:50 mixture of the *N*-butyl esters of 2,4,5-T and 2,4-dichlorophenoxyacetic acid [2,4-D]) used as a defoliant in the Vietnam War during 1962 to 1970 contained 2 to 30 ppm TCDD. TCDD has also been detected in the herbicide 2-(2,4,5-trichlorophenoxy)propionic acid (Silvex) and may be present in *o*-chlorophenol, 1,2,4,5-tetrachlorobenzene, Ronnel (fenchlorphos), and 2,4-D. Chlorophenoxy herbicides were banned from use on food crops, pastures, rice paddies, or rangelands in 1983, and the use of 2,4,5-T was completely banned in the United States (ATSDR 1998).

Exposure

CDDs and their structural analogues and usual co-contaminants (the polychlorinated dibenzofurans, or CDFs) are highly persistent and widespread environmental contaminants. Exposure to these compounds is typically expressed in terms of TCDD equivalents based on the concentrations and relative toxicity of the specific CDD and CDF congeners compared with TCDD. CDDs and CDFs have been detected in air, water, soil, sediments, and animal and human tissues. They are known to bioaccumulate throughout the food chain because of their lipophilic character and slow metabolism *in vivo*. TCDD is very persistent in the environment and readily accumulates in the food chain, because of its extreme lipophilicity.

The general population may be exposed to CDDs by inhalation, ingestion, and dermal contact. Foods are an important source of exposure (Schechter *et al.* 1997a). Meat, fish, and dairy products are the major source (> 90%) of human exposure to CDDs. The average daily intake of TCDD for a U.S. adult from meat alone was estimated at 23 pg, or approximately 50% of the total daily intake from food sources. The average daily intake of TCDD was 13 pg from milk, 5 pg from produce, and 5 pg from fish; however, for certain subpopulations (recreational and subsistence fishers), fish consumption may be the most important source of exposure. The maximum daily intake

of TCDD for residents of the Great Lakes region who regularly consumed fish was estimated to range from 390 to 8,400 pg. The developing fetus may be exposed to CDDs transferred across the placenta, and breastfed infants may be exposed to CDDs in their mother's milk. In the United States, breastfed infants might have been exposed to TCDD equivalents at 35 to 53 pg/kg of body weight per day through their mother's milk during their first year of life (ATSDR 1998).

Other pathways of exposure for the general population include inhalation of TCDD from municipal, medical, and industrial waste incinerators or other combustion processes (about 2% of daily intake) and ingestion of TCDD in drinking water (< 0.01% of daily intake). Fires involving capacitors or transformers containing chlorobenzene and PCBs are potential sources of CDDs. TCDD has been found in plastic packaging, clothes-dryer lint, vacuum-cleaner dust, room and car air filters, furnace-filter dust, and bleached paper products (ATSDR 1998). In a survey of 116 chemicals in blood and urine from 2,500 people across the United States in 1999 and 2000, the average concentration of TCDD was below the limit of detection for people of all ages (CEN 2003).

The U.S. Environmental Protection Agency's National Dioxin Study, conducted in the mid 1980s, detected TCDD at about 8% of urban sites and less than 1% of rural sites that were not expected to be contaminated with dioxins (i.e., background sites). The maximum concentration reported for these background sites was 11.2 ppt. However, soil concentrations in areas with past sources of TCDD contamination (i.e., hazardous-waste sites or sites where 2,4,5-TCP was produced and stored) typically were in the parts-per-billion range, with a maximum of about 2,000 ppm (ATSDR 1998). The data from the National Dioxin Study were consistent with concentrations of TCDD reported from previous studies of contaminated sites at Love Canal, in Niagara Falls, New York, and at various sites in Missouri that were sprayed for dust control in the early 1970s with dioxin-contaminated waste oil (Tiernan *et al.* 1985). TCDD concentrations in storm-sewer sediments collected at Love Canal in the late 1970s and early 1980s ranged from below detection (typically 10 to 100 ppt) to about 670 ppm. Concentrations of TCDD reported in the mid 1970s to early 1980s in soil from contaminated sites throughout Missouri, including the town of Times Beach, ranged from 4.4 to 1,750 ppb.

Both Love Canal and Times Beach were evacuated after the contamination was discovered. Love Canal was contaminated with many different organic and inorganic chemicals, but dioxins were the only chemicals of concern at Times Beach. Dioxin contamination at Times Beach was confirmed in November 1982; all residents (about 2,000 people) and businesses were permanently relocated, and all structures were torn down (EPA 2001). TCDD concentrations in some soil samples exceeded 100 ppb, with a maximum concentration of 317 ppb (Tiernan *et al.* 1985). More than 37,000 tons of dioxin-contaminated soil and other materials was removed from Times Beach and incinerated (EPA 2001). The ash residue from the incinerator was disposed of on site (on land), and all areas with residual dioxin concentrations between 1 and 20 ppb were covered with clean soil and revegetated (EPA 1988).

Occupational exposure to CDDs, including exposure of military personnel to Agent Orange in Vietnam, has been primarily through inhalation and dermal contact (ATSDR 1998). In occupations where CDDs may be present as contaminants (e.g., waste incineration; fire fighting; chemical research; paper bleaching; chlorophenoxy herbicide production, use, and disposal; or production and use of pentachlorophenol and other chlorinated compounds), workers may be at an increased risk of exposure; however, the number of workers potentially exposed to CDDs is not known.

Many studies of Vietnam veterans exposed to Agent Orange have been conducted (ATSDR 1998). Elevated exposure to TCDD was confirmed in the Air Force unit that was responsible for spraying herbicides in Vietnam (known as Operation Ranch Hand) (Pavuk *et al.* 2003). Operation Ranch Hand veterans were divided into three groups: background, low exposure, and high exposure. The mean serum TCDD concentration in the background group was 5.8 ppt and was not significantly different from that for a matched comparison group (4.6 ppt). Mean serum concentrations in the exposed groups were much higher, at 69.4 ppt (range = 18 to 617.8 ppt) in the high-exposure group and 15.6 ppt (range = 10 to 25.6 ppt) in the low-exposure group. Based on the biological half-life of TCDD, mean serum concentrations were extrapolated back to the end of the last tour of duty in Vietnam and were estimated at 55 ppt for the low-exposure group and 302.5 ppt for the high-exposure group.

Regulations

Department of Transportation (DOT)

TCDD is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

Mobile Source Air Toxics: Dioxin and furans are listed as a mobile-source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Regulations to limit dioxin emissions from various types of waste combustion and incineration units have been developed.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 5×10^{-9} µg/L; based on fish or shellfish consumption only = 5.1×10^{-9} µg/L.

Dioxin-containing wastes are prohibited from underground injection.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of TCDD = F020, F022, F023, F026, F027, F028, F032, K174.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 3×10^{-8} mg/L.

Toxic Substances Control Act

Manufacturers, importers, or processors of chemical substances specified under 40 CFR 766.25 must test for halogenated dibenzodioxins/dibenzofurans.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 3×10^{-8} mg/L.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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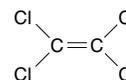
Tetrachloroethylene

CAS No. 127-18-4

Reasonably anticipated to be a human carcinogen

First listed in the *Fifth Annual Report on Carcinogens* (1989)

Also known as perchloroethylene or perc



Carcinogenicity

Tetrachloroethylene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Tetrachloroethylene caused tumors in two rodent species, at several different tissue sites, and by two different routes of exposure. Inhalation exposure to tetrachloroethylene caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice of both sexes and mononuclear-cell leukemia in rats of both sexes. In male rats, it also increased the combined incidence of benign and malignant tubular-cell kidney tumors, which are rare in rats (NTP 1986). Liver tumors were also observed in mice of both sexes administered tetrachloroethylene by stomach tube (NTP 1977, IARC 1979, 1987).

Cancer Studies in Humans

The data available from epidemiological studies were inadequate to evaluate the relationship between human cancer and exposure specifically to tetrachloroethylene at the time it was listed in the *Fifth Annual Report on Carcinogens*. A number of cohort and case-control studies of occupational exposure to tetrachloroethylene had been conducted. Although tetrachloroethylene may have been the predominant sol-

vent to which workers were exposed, coexposure to other chemicals (in particular trichloroethylene) among workers in the drycleaning industry was common (IARC 1982, 1987).

Since tetrachloroethylene was listed *Fifth Annual Report on Carcinogens*, additional epidemiological studies have been identified. Several ecological studies assessed cancer outcomes among residents exposed to groundwater contaminated with tetrachloroethylene, among other chemicals. The International Agency for Research on Cancer (IARC 1995) concluded that there was limited evidence for the carcinogenicity of tetrachloroethylene in humans, based mainly on evidence of consistent associations between tetrachloroethylene exposure and esophageal cancer, cervical cancer, and non-Hodgkin's lymphoma; however, confounding by exposure to other chemicals could not be ruled out, and the total numbers in the combined cohort studies were small.

Properties

Tetrachloroethylene is a halogenated alkene that exists at room temperature as a colorless liquid with a mildly sweet, ethereal odor (NTP 1986, HSDB 2009). It is only slightly soluble in water but is miscible with alcohol, ether, chloroform, benzene, and solvent hexane and soluble in most fixed and volatile oils. Tetrachloroethylene can be oxidized in air and sunlight and reacts with chemically active metals (e.g., barium or lithium) (IARC 1995). Physical and chemical properties of tetrachloroethylene are listed in the following table.

Property	Information
Molecular weight	165.8
Specific gravity	1.6227 at 20°C/4°C
Melting point	-22.3°C
Boiling point	121.3°C
Log K_{ow}	3.4
Water solubility	206 mg/L at 25°C
Vapor pressure	18.5 mm Hg at 25°C
Vapor density relative to air	5.7

Source: HSDB 2009.

Use

Tetrachloroethylene is used primarily as a cleaning solvent and as a chemical precursor for fluorocarbons. In the 1970s, domestic use patterns were as follows: 58% for drycleaning and textile processing, 18% for metal cleaning, 12% for chemical intermediates, and 12% for all other uses (IARC 1995). During the 1990s, tetrachloroethylene use in the drycleaning industry declined in order to meet stringent government regulations for workplace exposure. By 2002, uses were 15% for drycleaning, 10% for metal cleaning, 65% for chemical intermediates, and 10% for other uses (CMR 2002). Tetrachloroethylene also has been used as an insulating fluid and cooling gas in electrical transformers; in paint removers, printing inks, adhesive formulations, paper coatings, and leather treatments; in aerosol formulations, such as water repellents, automotive cleaners, silicone lubricants, and spot removers; as an extractant for pharmaceuticals; to remove soot from industrial boilers; and as an antihelminthic agent (IARC 1995).

Production

Tetrachloroethylene was first prepared in 1821, and commercial production in the United States began in 1925. Several commercial grades are available that differ in the amount and type of added stabilizers (e.g., amines, phenols, and epoxides). Annual production rose rapidly in the United States from 5,000 metric tons (1.1 million pounds) in 1941 to a peak of 347,000 metric tons (763 million pounds) in 1980. From 1980 to 1993, annual production declined by more than 60% (IARC 1995, ATSDR 1997), but from 1996 to 1999, U.S. de-

mand (domestic production plus imports) increased from 280 million pounds to 318 million pounds. In 2002, the combined production capacity of the three U.S. manufacturers of tetrachloroethylene was 430 million pounds (CMR 2002). In 2009, tetrachloroethylene was produced by 15 manufacturers worldwide, including 3 U.S. manufacturers (SRI 2009), and was available from 115 suppliers, including 43 U.S. suppliers (ChemSources 2009).

U.S. imports of tetrachloroethylene were 132 million pounds in 1977, 38 million pounds in 1982, and 140 million pounds in 1985 (HSDB 2009). Imports averaged 80 million pounds from 1992 to 1996 and 36 million pounds from 1998 to 2000, reaching a maximum of 72.4 million pounds in 2003 (USITC 2009). In 2008, imports were 36.2 million pounds. U.S. exports of tetrachloroethylene totaled 64 million pounds in 1978, 54 million pounds in 1983, and 22 million pounds in 1985. Exports averaged 45 million pounds from 1992 to 1996, increasing to an average of 50 million pounds from 1998 to 2008 (HSDB 2009).

Exposure

Tetrachloroethylene is widely distributed in the environment, because it is released from many industrial processes and consumer products. The primary routes of potential human exposure to tetrachloroethylene are inhalation and ingestion of contaminated water or food. Dermal exposure also may occur, but is not important for the majority of the population (ATSDR 1997). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, total environmental releases of tetrachloroethylene declined by almost 94% from 37.7 million pounds in 1988 to 2.2 million pounds in 2008. In 2008, most of the releases, from 225 facilities, were to air (TRI 2010). Numerous studies have detected tetrachloroethylene in the air in the United States in rural, urban, and industrial areas. Typical concentrations in rural and remote areas were in the low parts-per-trillion range, while concentrations in urban and industrial areas were in the high parts-per-trillion to low parts-per-billion range.

Studies conducted in New York City measured ambient indoor-air concentrations of tetrachloroethylene in apartments and in a day-care facility located in buildings containing drycleaning facilities (Schreiber *et al.* 2002). Concentrations of tetrachloroethylene were much higher in the buildings with drycleaning facilities than in buildings without such facilities. Tetrachloroethylene levels were measured in exhaled breath by personal monitoring devices and in samples of blood from individuals living in apartments over drycleaning facilities. Concentrations of tetrachloroethylene were elevated in samples from exposed individuals. The general population may also be exposed to tetrachloroethylene through use of coin-operated laundromats that contain drycleaning machines or through exposure to freshly drycleaned clothing. Studies show elevated concentrations of tetrachloroethylene in laundromats (even months after removal of the drycleaning machines). Tetrachloroethylene concentrations in homes with freshly drycleaned clothing stored in the closets may be 2 to 30 times higher than average background levels. In addition, workers in the drycleaning industry may carry tetrachloroethylene home on their person or clothes and therefore serve as a source of exposure of their families. In one study, indoor air concentrations of tetrachloroethylene in apartments where drycleaning workers lived were over 10 times the levels in other apartments in the same buildings, where the occupants were not employed by drycleaning facilities (ATSDR 1997).

Tetrachloroethylene may also be formed in small quantities during chlorination of water. EPA estimated that in 1985, 11.4 million people were exposed to tetrachloroethylene at concentrations of at least 0.5 µg/L and 874,000 were exposed to concentrations of at least

5 µg/L from municipal water supplies in the United States (IARC 1995). Contamination of drinking water with tetrachloroethylene was reported in the Cape Cod, Massachusetts, area in the late 1970s (Webler and Brown 1993). The chemical leached from the vinyl lining of asbestos-cement water distribution pipes. The highest level reported was 18 mg/L from a pipe in Falmouth, Massachusetts, but levels of 1,600 to 7,750 µg/L were reported for pipes running along dead-end streets (Wakeham *et al.* 1980, Aschengrau *et al.* 2003). Tetrachloroethylene has also been detected in rainwater, sea water, rivers, ground-water, commercial deionized charcoal-filtered water, dairy products, meats, oils and fats, beverages, fruits and vegetables, fresh bread, fish, shellfish, marine mammals, glues, printing inks, lubricants, stain and paint removers, and other consumer products (IARC 1995, ATSDR 1997). It has even been detected in snow in Antarctica (Zoccolillo *et al.* 2007). It was detected in 67 items in the U.S. Food and Drug Administration's Total Diet Study (FDA 2006).

Workers involved in drycleaning, metal degreasing, and fluorocarbon production are likely to be exposed to tetrachloroethylene. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 688,000 workers in 49,025 U.S. facilities potentially were exposed to tetrachloroethylene (NIOSH 1990). A 1994 survey prepared by industry estimated that 450,000 workers potentially were exposed (IARC 1995). Occupational exposure has trended lower over the past several decades. Typical tetrachloroethylene concentrations in workplace air at drycleaning facilities were 350 to 700 mg/m³ (about 50 to 100 ppm) in the 1970s and 70 to 350 mg/m³ (about 10 to 50 ppm) in the 1980s (IARC 1995). The highest exposures occur during loading and unloading of the drycleaning machines. More recent studies by the National Institute for Occupational Safety and Health indicated that exposure levels in the drycleaning industry were below the recommended occupational exposure guideline of 25 ppm (ATSDR 1997). In 2003, the mean concentration of tetrachloroethylene at U.S. drycleaning facilities was 3.8 ppm (Toraason *et al.* 2003).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of tetrachloroethylene on ships and barges.

Consumer Product Safety Commission (CPSC)

Visual novelty devices containing tetrachloroethylene have labeling requirements.

Department of Transportation (DOT)

Tetrachloroethylene is considered a hazardous material and a marine pollutant, and special requirements have been set for marking, labeling, and transporting this material, including transporting it in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of tetrachloroethylene is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent guidelines: Listed as a toxic pollutant.

Water quality criteria: Based on fish or shellfish and water consumption = 0.69 µg/L; based on fish or shellfish consumption only = 3.3 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.7 mg/L. *Listed Hazardous Waste:* Waste codes for which the listing is based wholly or partly on the presence of tetrachloroethylene = U210, F001, F002, F024, F025, K016, K019, K020, K073, K116, K150, K151.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 100 ppm.

Ceiling concentration = 200 ppm (5 min in any 3 h).

Acceptable peak exposure = 300 ppm.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 25 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 100 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommends that workplace exposure levels of substance be minimized.

Immediately dangerous to life and health (IDLH) limit = 150 ppm.

Listed as a potential occupational carcinogen.

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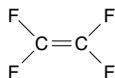
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Tetrafluoroethylene

CAS No. 116-14-3

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)



Carcinogenicity

Tetrafluoroethylene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals (NTP 1997).

Cancer Studies in Experimental Animals

Exposure to tetrafluoroethylene by inhalation caused tumors at several different tissue sites in mice and rats. It caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in mice and rats of both sexes and blood-vessel tumors (hemangioma and hemangiosarcoma) in the liver of mice of both sexes and female rats. Tetrafluoroethylene also increased the combined incidence of benign and malignant kidney tumors (renal-tubule adenoma and carcinoma) in rats of both sexes and caused mononuclear-cell leukemia in female rats. In addition, it caused cancer of the immune system (histiocytic sarcoma) in numerous organs and tissues in mice of both sexes (NTP 1997).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to tetrafluoroethylene.

Studies on Mechanisms of Carcinogenesis

Tetrafluoroethylene did not cause gene mutations in *Salmonella typhimurium* with or without mammalian metabolic activation (NTP 1997, HSDB 2009). It also did not cause gene mutations in Chinese hamster ovary cells or micronucleus formation in peripheral-blood erythrocytes in mice exposed *in vivo* (NTP 1997). In tetrafluoroethylene-induced hepatocellular tumors from B6C3F₁ mice, mutations in codon 61 of the *H-ras* oncogene occurred at a significantly lower frequency (15%) than in spontaneous liver tumors (56% to 59%), suggesting that tetrafluoroethylene causes liver tumors via a *ras*-independent pathway (NTP 1997).

The kidney-specific toxicity and carcinogenicity of tetrafluoroethylene most likely are related to the selective uptake and subsequent processing of tetrafluoroethylene-glutathione conjugates by renal β -lyase (Anders *et al.* 1988, Miller and Surh 1994). In rats, a tetrafluoroethylene-cysteine conjugate is bioactivated in the kidney to a difluorothionacetyl fluoride, the putative reactive metabolite for tetrafluoroethylene-induced nephrotoxicity (NTP 1997). There is no evidence to suggest that mechanisms by which tetrafluoroethylene causes tumors in experimental animals would not also operate in humans.

Properties

Tetrafluoroethylene is a halogenated olefin that occurs as a colorless, odorless gas at room temperature. It is practically insoluble in water. Tetrafluoroethylene is very flammable and may present a fire hazard. At high pressures, it may polymerize easily without an inhibitor, especially if heated or in the presence of oxygen (IARC 1979, NTP 1997). Physical and chemical properties of tetrafluoroethylene are listed in the following table.

Property	Information
Molecular weight	100.0 ^a
Density	1.519 g/cm ³ at -76°C ^a
Melting point	-142.5°C ^a
Boiling point	-75.9°C ^a
Log <i>K</i> _{ow}	1.21 ^b
Water solubility	0.16 g/L at 25°C ^a
Vapor pressure	2.45 × 10 ⁴ mm Hg at 25°C ^b
Vapor density relative to air	3.87 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Tetrafluoroethylene is used primarily in the synthesis of fluoropolymers, particularly the homopolymer polytetrafluoroethylene (PTFE, or Teflon) (IARC 1979, HSDB 2009). Tetrafluoroethylene is also used as a copolymer to make fluorinated ethylene-propylene resins with hexafluoropropylene as a copolymer, perfluoroalkoxy resins with perfluoropropyl vinyl ether as the copolymer, and ethylene-tetrafluoroethylene resins. Tetrafluoroethylene is used in the production of low-molecular-mass compounds and intermediates, such as iodo-perfluoroalkanes, and it reacts with perfluoronitrosoalkanes to produce nitroso rubbers (HSDB 2009). Tetrafluoroethylene was also used in the past in food-product aerosols.

Production

Tetrafluoroethylene is produced primarily by the pyrolysis of chlorodifluoromethane or trifluoromethane (NTP 1997). It was first produced commercially in the United States in 1960 (IARC 1979). In 2009, tetrafluoroethylene was produced by three manufacturers in China (SRI 2009) and was available from six suppliers, including two U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of tetrafluoroethylene totaled 10 million to 50 million pounds from 1986 to 1994, increasing to between 50 million and 100 million pounds from 1998 to 2006 (EPA 2004, 2009).

Exposure

Inhalation is the primary route of exposure to tetrafluoroethylene; however, exposure from ingestion and dermal contact are also possible. Although human exposure to tetrafluoroethylene is mainly occupational, it may also occur through release of tetrafluoroethylene to the environment. Tetrafluoroethylene may be released to the environment during its production and use in the production of fluoropolymers, nitroso rubbers, and low-molecular-mass compounds and intermediates (HSDB 2009). However, reporting of releases of tetrafluoroethylene is not required under EPA's Toxics Release Inventory system. Tetrafluoroethylene has been reported, along with several other low-molecular-mass halogenated compounds, in volcanic emissions (Gribble 1994). If released to air, tetrafluoroethylene will exist in the vapor phase and react with photochemically produced hydroxyl radicals and ozone. If released to water or soil, it is not expected to bind to soil or sediment. It is expected to volatilize rapidly

from water surfaces, with a half-life of 2.9 hours in a river model and 4 days in a lake model. Tetrafluoroethylene has a low potential for bioconcentration, and it does not biodegrade or hydrolyze rapidly.

Occupational exposure to tetrafluoroethylene may occur among workers involved in the production of polymers and copolymers of products containing the chemical (HSDB 2009). Tetrafluoroethylene is produced and maintained in closed-capture systems, so exposure would occur primarily through leakage from these systems or from pyrolysis of Teflon or other polymers (NTP 1997). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 14,963 employees (in 870 facilities in the Paper and Allied Products, Printing and Publishing, and Transportation Equipment industries), including 325 women, potentially were exposed to tetrafluoroethylene (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Tetrafluoroethylene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Occupational Safety and Health Administration (OSHA)

Considered a highly hazardous chemical: Threshold quantity (TQ) = 5,000 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm.

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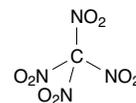
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Tetranitromethane

CAS No. 509-14-8

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)



Carcinogenicity

Tetranitromethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to tetranitromethane by inhalation caused lung tumors in rats and mice. In rats and mice of both sexes, it caused benign and malignant lung tumors (alveolar/bronchiolar adenoma and carcinoma); the tumors were predominantly malignant, and many of them metastasized, to a variety of organs. Exposure to tetranitromethane also caused a rare form of lung cancer (squamous-cell carcinoma) in rats of both sexes; at the time of the study, squamous-cell carcinoma had not been observed in unexposed female historical controls (~1,600) and had been observed in only 3 of 1,600 unexposed male controls (NTP 1990, Bucher *et al.* 1991).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to tetranitromethane.

Properties

Tetranitromethane is a nitroalkane compound that is a pale-yellow liquid with a biting, acrid odor at room temperature (IARC 1996, HSDB 2009). It is soluble in alcoholic potassium hydroxide, ethanol, and diethyl ether, and insoluble in water. Tetranitromethane is highly explosive when subjected to heat or shock and forms sensitive and powerful explosives when mixed with certain oxygen-deficient explosives or hydrocarbons (IARC 1996). Physical and chemical properties of tetranitromethane are listed in the following table.

Property	Information
Molecular weight	196.0 ^a
Specific gravity	1.6229 at 20°C/4°C ^a
Melting point	13.8°C ^a
Boiling point	126°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	-0.791 ^a
Water solubility	85 g/L at 25°C ^b
Vapor pressure	8.42 mm Hg at 25°C ^a
Vapor density relative to air	0.8 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Tetranitromethane is used as an oxidizer in rocket propellants, in the manufacture of liquid explosives, and as an additive to increase the cetane number of diesel fuel (NTP 1990, IARC 1996, OSHA 2007). It is also used as a reagent for detecting the presence of double bonds in organic compounds and as a mild nitrating reagent, reacting with tyrosine in proteins and peptides. It was proposed as a surface disinfectant against viruses (Singh *et al.* 1994), based on data suggest-

ing that it was useful against enveloped and nonenveloped viruses and many other microbial infective agents.

Production

In Germany during World War II, attempts were made to synthesize large amounts of tetranitromethane for use as a substitute for nitric acid in rocket fuel. The method, which involved the nitration of acetic anhydride with nitric acid, allowed a production rate of up to 10 tons within a "few weeks," but the process was costly. By the end of the war, a less expensive method using acetylene and nitric acid was devised, with a reported production capacity of 10 kg/day (NTP 1990). No current estimates of commercial production of tetranitromethane were found. In 2009, tetranitromethane was available from six suppliers worldwide, including four U.S. suppliers (ChemSources 2009).

Exposure

The routes of potential human exposure to tetranitromethane are inhalation, ingestion, and eye or skin contact (OSHA 2007). Tetranitromethane may be released into the environment during its manufacture and use as a rocket fuel, diesel fuel booster, organic reagent, or explosive in mixture with toluene (HSDB 2009). It was reported to be an air pollutant emitted as a by-product of production of explosives in U.S. government factories; the estimated worst-case tetranitromethane level in the vicinity of the factories was 20 mg/m³ (approximately 2.5 ppm). Occupational exposure to tetranitromethane presumably occurred during the manufacture and use of trinitrotoluene (TNT) (NTP 1990). During the early part of World War I, a high incidence of "TNT intoxication" occurred in U.S. and British facilities involved in TNT production; an additional step involving washing the crude material with a sodium sulfite solution to hydrolyze the tetranitromethane was introduced to alleviate this problem (NTP 1990). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,445 workers, including 230 women, potentially were exposed to tetranitromethane (NIOSH 1990).

Regulations

Department of Transportation (DOT)

Tetranitromethane is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Reportable quantity (RQ) = 10 lb.

Threshold planning quantity (TPQ) = 500 lb.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of tetranitromethane = P112.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 1 ppm (8 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.005 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm (8 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 4 ppm.

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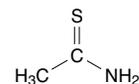
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Thioacetamide

CAS No. 62-55-5

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Thioacetamide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to thioacetamide caused tumors in two rodent species and at two different tissue sites. Dietary administration of thioacetamide caused liver cancer (hepatocellular carcinoma) in mice of both sexes and in female rats and tumors of the bile duct (cholangiocellular tumors) in rats of both sexes (IARC 1974). Since thioacetamide was listed in the *Third Annual Report on Carcinogens*, an additional study has been identified, which found that thioacetamide administered in the diet also caused liver cancer (hepatocellular carcinoma and papillary adenocarcinoma) in male rats (Kuroda *et al.* 1987).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to thioacetamide

Properties

Thioacetamide is a thioamide compound that exists at room temperature as colorless to yellow crystals with a slight odor of mercaptans (IARC 1974, HSDB 2009). It is soluble in water and ethanol, miscible with benzene and petroleum ether, and sparingly soluble in ether. It is hydrolyzed by acids or bases and reacts with salts of heavy metals. Physical and chemical properties of thioacetamide are listed in the following table.

Property	Information
Molecular weight	75.1 ^a
Specific gravity	1.336 g/cm ^{3b}
Melting point	113°C to 114°C ^a
Log <i>K</i> _{ow}	-0.26 ^a
Water solubility	163 g/L at 25°C ^a
Vapor pressure	15.2 mm Hg at 25°C ^c
Dissociation constant (p <i>K</i> _a)	13.4 ^a

Sources: ^aHSDB 2009, ^bAkron 2009, ^cChemIDplus 2009.

Use

Thioacetamide has been used as an organic solvent in the leather, textile, and paper industries, as an accelerator in the vulcanization of buna rubber (synthetic polybutadiene), and as a stabilizer of motor fuel. However, there is no evidence that it is currently used for any of these purposes. Currently, thioacetamide is used only as a replacement for hydrogen sulfide in qualitative analyses (IARC 1974, HSDB 2009) and as a reactant in making metal salt nanoparticles (Zhang *et al.* 2002, Liddell and Summers 2004, Liu *et al.* 2004, Jin *et al.* 2006, Yang *et al.* 2006, Zhou *et al.* 2006).

Production

Synthesis of thioacetamide in the United States was first reported in 1921 (IARC 1974). U.S. production in 1977 was at least 1,000 lb; however, there was no evidence of commercial production in 1982 (HSDB 2009). In 2009, thioacetamide was produced by seven manufacturers in India and one manufacturer in East Asia (SRI 2009) and was available from 45 suppliers, including 26 U.S. suppliers (ChemSources 2009). No information was found on U.S. imports or exports of thioacetamide.

Exposure

The primary routes of potential human exposure to thioacetamide are inhalation and dermal contact (HSDB 2009). Consumers could have been exposed to thioacetamide residues through contact with products for which it was used as a solvent in the manufacturing process. According to the U.S. Environmental Protection Agency's Toxics Release Inventory, 500 lb of thioacetamide was released to the environment in 1988. Since then, releases have not exceeded 264 lb, and no releases were reported for three years. In 2007, one facility released 10 lb of thioacetamide to an off-site hazardous-waste landfill (TRI 2009).

Occupational exposure may occur during production and use of thioacetamide (HSDB 2009). The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 1,130 workers potentially were exposed to thioacetamide (NIOSH 1976). Clinical laboratory technicians are at greatest risk of exposure according to the National Occupational Exposure Survey (conducted from 1981 to 1983), which estimated that 786 workers, including 592 women, potentially were exposed to thioacetamide (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of thioacetamide = U218.

Listed as a hazardous constituent of waste.

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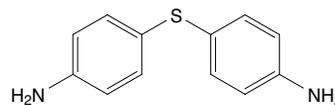
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4,4'-Thiodianiline

CAS No. 139-65-1

Reasonably anticipated to be a human carcinogen

First listed in the *Eleventh Report on Carcinogens* (2004)



Carcinogenicity

4,4'-Thiodianiline is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 4,4'-thiodianiline caused tumors at several different tissue sites in mice and rats. Dietary administration of 4,4'-thiodianiline caused thyroid-gland cancer (follicular-cell carcinoma) in mice and rats of both sexes and liver cancer (hepatocellular carcinoma) in mice of both sexes and in male rats (NCI 1978). In rats, 4,4'-thiodianiline also caused cancer of the uterus (adenocarcinoma) in females and increased the combined incidence of benign and malignant tumors of the ear canal (Zymbal gland) in males. In addition, colon tumors in male rats and Zymbal-gland tumors in female rats were considered to be related to 4,4'-thiodianiline exposure because

of the rarity of these types of tumors (NCI 1978, Cueto and Chu 1979). In studies with *ras*H2 transgenic mice (which carry a human gene that increases their susceptibility to cancer), dietary exposure to 4,4'-thiodianiline caused increased proliferation of thyroid follicular cells and benign thyroid-gland tumors (follicular-cell hyperplasia and adenoma) in transgenic mice and their nontransgenic littermates (Yamamoto *et al.* 1998a,b).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4,4'-thiodianiline.

Studies on Mechanisms of Carcinogenesis

4,4'-Thiodianiline caused mutations in some strains of *Salmonella typhimurium* (TA98 and TA100) but not others (TA1535 and TA1537). 4,4'-Thiodianiline orally administered to mice caused DNA damage in the brain, liver, urinary bladder, and lungs. In rats, 4,4'-thiodianiline binds to hemoglobin as both the diamine and the *N*-acetylamine. Among several bicyclic diamines studied (including 4,4'-thiodianiline), the extent of hemoglobin binding was positively correlated with carcinogenic potency (IARC 1982). Studies of the relationship between chemical structure and carcinogenic activity have suggested that the aryl-amino group of 4,4'-thiodianiline is most likely involved in its carcinogenicity. Three other dianiline compounds listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens* — 4,4'-oxydianiline, 4,4'-methylenedianiline, and 4,4'-methylenebis(2-chloroaniline) — cause some of the same types of tumors in animals as 4,4'-thiodianiline does.

Properties

4,4'-Thiodianiline is an aromatic amine that exists as brown powder or needles at room temperature. It is very slightly soluble in water and very soluble in alcohol, ether, and hot benzene. 4,4'-Thiodianiline is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 4,4'-thiodianiline are listed in the following table.

Property	Information
Molecular weight	216.3 ^a
Melting point	108°C to 109°C ^a
Boiling point	361°C ^b
Log <i>K</i> _{ow}	2.18 ^b
Water solubility	0.310 g/L at 25°C ^b
Vapor pressure	1.11 × 10 ⁻⁵ mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

4,4'-Thiodianiline was used almost exclusively as a chemical intermediate in the production of three dyes: C.I. mordant yellow 16, milling red G, and milling red FR. However, only mordant yellow 16 had any commercial significance in the United States (IARC 1982, HSDB 2009); it was used to dye wool and for printing on wool, silk, and cotton (SDC 1971). Mordant yellow 16 has been used as an indicator in the U.S. government's nerve gas detector program (SOCMA 2002). However, no uses of either 4,4'-thiodianiline or mordant yellow 16 since the early 1990s have been reported.

Production

4,4'-Thiodianiline is prepared by reaction of aniline with sulfur (IARC 1982, HSDB 2009). U.S. production was first reported for 1941 to 1943 (IARC 1982); however, 4,4'-thiodianiline is no longer produced in the United States. The U.S. Dye Manufacturers Operating Committee of

the Ecological and Toxicological Association of Dyes and Organic Pigments Manufacturers speculated in 2002 that only a few hundred pounds of 4,4'-thiodianiline were imported into the United States each year (SOCMA 2002). U.S. production of mordant yellow 16 was last reported for 1991 (USITC 1993). Separate production statistics for mordant yellow 16 were not available; however, total mordant dye production was 33,100 kg (73,000 lb) in 1987, 29,000 kg (64,000 lb) in 1989, and 9,000 kg (19,800 lb) in 1990 (USITC 1988, 1990, 1991). In 2009, 4,4'-thiodianiline was produced in China (SRI 2009) and was available from 15 U.S. suppliers (ChemSources 2009). One U.S. producer of mordant yellow 16 was identified in 1983 and 1984 (SRI 1983, 1984), but none in 2009 (SRI 2009).

Exposure

Dye workers may have been exposed to 4,4'-thiodianiline through skin contact, accidental ingestion, or inhalation.

Regulations

Environmental Protection Agency (EPA)

Emergency Planning and Community Right-To-Know Act
Toxics Release Inventory: Listed substance subject to reporting requirements.

Department of Transportation (DOT)

Toxic dyes and toxic dye intermediates are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

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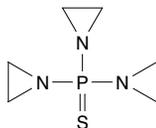
Thiotepa

CAS No. 52-24-4

Known to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as tris(1-aziridinyl)phosphine sulfide



Carcinogenicity

Thiotepa is *known to be a human carcinogen* based on sufficient evidence from studies in humans. Thiotepa was first listed in the *Second Annual Report on Carcinogens* in 1981 as *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and insufficient evidence of carcinogenicity from studies in humans. Thiotepa was reclassified as *known to be a human carcinogen* in the *Eighth Report on Carcinogens* in 1998.

Cancer Studies in Humans

Exposure to thiotepa is specifically associated with leukemia in humans. Adamson and Seiber (1981) summarized nine case reports from 1970 to 1978 of secondary development of nonlymphocytic leukemia in patients with primary cancer at other sites who had received only thiotepa as a therapeutic agent. Additional evidence was provided by a case-control study which found that patients treated with thiotepa were significantly more likely to develop secondary leukemia than those undergoing surgery alone (IARC 1990).

Cancer Studies in Experimental Animals

Thiotepa administered by intraperitoneal injection caused lymphoma and/or leukemia (lymphocytic or granulocytic) in mice of both sexes and in male rats. It also caused benign lung tumors in mice of both sexes, cancer of the mammary gland and uterus in female rats, cancer of the skin or ear canal (squamous-cell carcinoma) in rats of both sexes and in male mice, and cancer of the preputial gland (squamous-cell carcinoma) in male mice (IARC 1975, 1990, NCI 1978). In male rats administered thiotepa by intravenous injection, cancer occurred at numerous tissue sites, including the abdominal cavity, mammary gland, blood vessels, bone marrow, lymphatic system, salivary glands, adrenal gland, and testis (IARC 1975, 1987, 1990).

Studies on Mechanisms of Carcinogenesis

Thiotepa and its major metabolite, tris(aziridinyl)phosphine oxide (also called TEPA or triethylenephosphoramidate) are direct alkylating agents with potent genotoxic activity in a wide variety of prokaryotic, lower eukaryotic, and mammalian *in vitro* and *in vivo* test systems. Thiotepa's ability to cause DNA damage, mutations, micronucleus formation, and/or chromosomal aberrations in somatic and germ cells from exposed rodents, rabbits, and nonhuman primates and chromosomal aberrations in peripheral-blood lymphocytes from treated humans is consistent with its being a genotoxic carcinogen (IARC 1990).

Properties

Thiotepa is an ethyleneimine alkylating agent (NCI 1978) that is a white crystalline solid with a faint odor at room temperature. It is soluble in water, alcohol, benzene, ether, and chloroform. It is un-

stable in light and in acidic solution, but stable in alkaline solutions (IARC 1990). Physical and chemical properties of thiotepa are listed in the following table.

Property	Information
Molecular weight	189.2 ^a
Melting point	51.5°C ^a
Log K_{ow}	0.53 ^b
Water solubility	190 g/L at 25°C ^b
Vapor pressure	0.00845 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Thiotepa suppresses cell growth and division and was introduced in 1953 for use in cancer chemotherapy to treat lymphoma and a variety of solid and soft-tissue tumors. It was commonly used in cancer therapy until the early 1970s (only 3 kg of thiotepa was used in 1973). Although thiotepa has largely been replaced by the nitrogen mustards, it still has specific uses, particularly as a component of experimental high-dose chemotherapy regimens. Thiotepa was most effective in treating adenocarcinoma of the breast, ovary, and bladder, malignant lymphoma, bronchiogenic carcinoma, and Wilms' tumor. By the late 1980s, thiotepa was also used at high doses in combination chemotherapy with cyclophosphamide in patients with refractory malignancies treated with autologous bone transplantation (IARC 1975, 1990). As of 2009, thiotepa was used to treat a variety of cancers, including lymphoma and cancer of the bladder, ovary, breast, lung, and brain (MedlinePlus 2009).

Thiotepa was tested for use as an intermediate in the manufacture of polymeric flame retardants for cotton, and it was shown to be an effective insect chemosterilant. However, these uses were not developed for commercial application because of various problems associated with its application, toxicity, and environmental effects (IARC 1975).

Production

One U.S. company produced thiotepa in the early 1970s, but by 1990, it was produced only in Japan (IARC 1975, 1990). In 2009, thiotepa was produced by one manufacturer, in East Asia (SRI 2009), and was available from four U.S. suppliers (ChemSources 2009). Three U.S. pharmaceutical companies produced four drug products approved by the U.S. Food and Drug Administration that contained thiotepa as the active ingredient (FDA 2009). No data on current or past production or U.S. import or export volumes were found.

Exposure

Individuals are exposed to thiotepa during its use in cancer therapy. Thiotepa has been administered through various parenteral routes (e.g., intravenous, intramuscular, intrathecal, and intratumoral); generally, adjustment of the dosage is based on changes in leukocyte counts. Thiotepa is available in injectable form in solutions containing 15 or 30 mg per vial (FDA 2009). The initial dose typically is 5 to 40 mg (3 to 23 mg/m² of body surface area) administered at one- to four-week intervals; doses up to 75 mg/m² have been used in children. Daily doses in excess of 1,100 mg/m² have been used in high-dose therapy (IARC 1990).

Occupational exposure may occur among health-care professionals who prepare and administer thiotepa in cancer therapy and among workers involved in its formulation and packaging. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 11,452 workers, including 8,724 women, potentially were exposed to thiotepa (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Thiotepa is a prescription drug subject to labeling and other requirements.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

Occupational Safety and Health Administration (OSHA)

A comprehensive set of guidelines has been established to prevent occupational exposures to hazardous drugs in health-care settings.

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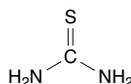
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Thiourea

CAS No. 62-56-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

Thiourea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Thiourea caused tumors in rats at several different tissue sites and by two different routes of exposure. Administration of thiourea in the drinking water caused benign and malignant thyroid-gland tumors (adenoma and carcinoma) in both sexes and cancer of the Zymbal gland (squamous-cell carcinoma) in males. Dietary administration

caused benign liver tumors (hepatocellular adenoma) in rats of unspecified sex, and intraperitoneal injection followed by administration in the drinking water caused cancer of the Zymbal gland (squamous-cell carcinoma or mixed-cell sarcoma) in rats of both sexes (IARC 1974).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to thiourea.

Properties

Thiourea is a diamide of thiocarbonic acid and occurs as white or almost colorless crystals at room temperature (Akron 2009, HSDB 2009). It is soluble in cold water, alcohol, and ammonium thiocyanate, and sparingly soluble in ether (HSDB 2009). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of thiourea are listed in the following table.

Property	Information
Molecular weight	76.1 ^a
Specific gravity	1.405 ^a
Melting point	176°C to 178°C ^a
Boiling point	sublimes <i>in vacuo</i> at 150°C to 160°C ^a
Log K_{ow}	-1.08 ^a
Water solubility	142 g/L at 25°C ^a
Vapor pressure	2.8×10^{-3} mm Hg at 25°C ^a
Dissociation constant (pK_a)	2.03 at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

The most common uses for thiourea have been for the production of thiourea dioxide (30%), in leaching of gold and silver ores (25%), in diazo papers (15%), and as a catalyst in the synthesis of fumaric acid (10%) (IARC 2001). It has also been used in the production and modification of synthetic resins. Other uses of thiourea are as a photographic toning agent, in hair preparations, as a drycleaning agent, in the synthesis of pharmaceuticals and pesticides, in boiler-water treatment, and as a reagent for bismuth and selenite ions. It has also been used in textile and dyeing auxiliaries, in the production of industrial cleaning agents (e.g., for photographic tanks and metal surfaces in general), for engraving metal surfaces, as an isomerization catalyst in the conversion of maleic to fumaric acid, in copper-refining electrolysis, in electroplating, and as an antioxidant. Other uses have included as a vulcanization accelerator, an additive for slurry explosives, as a viscosity stabilizer for polymer solutions, and as a mobility buffer in petroleum extraction. It is also used as an ingredient of consumer silver polishes (HPD 2009), and has been used in the removal of mercury from wastewater by chlorine-alkali electrolysis (IARC 1974, 2001, WHO 2003).

Production

Commercial production of thiourea in the United States began in 1938 (IARC 1974). In 1993, global production of thiourea was about 10,000 metric tons (22 million pounds) (WHO 2003). In 2009, thiourea was produced by 19 manufacturers worldwide, none in the United States (SRI 2009), and was available from 81 suppliers, including 33 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule between 1986 and 1998 indicated that U.S. production plus imports of thiourea totaled between 1 million and 10 million pounds; in 2002, the quantity fell to between 500,000 and 1 million pounds (EPA 2004).

Exposure

The routes of potential human exposure to thiourea are inhalation and dermal contact (HSDB 2009). There is a small risk of consumer exposure to thiourea in silver-tarnish removers, in which it is present at concentrations of up to 7% (HPD 2009). Thiourea may also be present in animal-hide glues and in diazo-treated papers, such as blueprints (WHO 2003). Thiourea has been found to occur naturally in laburnum shrubs and as a metabolite of the fungi *Verticillium albo-atrum* and *Bortrylio cinerea* (IARC 1974).

If released to air, thiourea is expected to remain in the vapor phase and to react with photochemically produced hydroxyl radicals, with a half-life of 2.4 hours. It has not been measured in ambient air (WHO 2003). If released to surface water, thiourea is expected to remain in the dissolved phase and to degrade with a half-life of 17 days. If released to soil, thiourea may leach to groundwater. It has been detected in one sample of groundwater in Germany at a concentration of 130 mg/L. According to EPA's Toxics Release Inventory, environmental releases of thiourea from 1988 to 2007 ranged from a high of 44,455 lb in 2001 (of which over 31,000 lb was released to an on-site hazardous-waste landfill) to a low of 1,333 lb in 2007, of which most was released to on-site surface impoundments (500 lb) or to air (513 lb) (TRI 2009).

Workers may be exposed to thiourea during its production or use (HSDB 2009). The National Occupational Exposure Survey (conducted 1981 to 1983) estimated that 37,571 workers, including 10,969 women, potentially were exposed to thiourea (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of thiourea = U219.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Thiourea is not permitted in food for human consumption.

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Tobacco-Related Exposures

Introduction

Tobacco contains more than 2,500 chemical constituents, many of which are known human carcinogens. Tobacco smoking produces both mainstream smoke, which is drawn through the tobacco column and exits through the mouthpiece during puffing, and sidestream smoke, which is emitted from the smoldering tobacco between puffs. Chewing tobacco and snuff are the two main forms of smokeless tobacco used in the United States. Tobacco smoking, environmental tobacco smoke, and smokeless tobacco were first listed (separately) in the *Ninth Report on Carcinogens* (2000). The profiles for each of these substances and exposure circumstances, which are listed (separately) as *known to be a human carcinogen*, follow this introduction.

Tobacco Smoking

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Tobacco smoking is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Tobacco smoking has been shown to cause cancer of the lung, urinary bladder, renal pelvis, oral cavity, pharynx, larynx, esophagus, lip, and pancreas in humans (IARC 1986). The risk of death from lung cancer increases with increasing duration of smoking and with increasing numbers of cigarettes smoked. Smoking cessation avoids the increased risk associated with continued smoking. The carcinogenic effects of tobacco smoke are increased in individuals with certain predisposing genetic polymorphisms (i.e., which code for different forms of the metabolic enzyme microsomal monooxygenase). Since tobacco smoking was first listed in the *Ninth Report on Carcinogens* in 2000, the International Agency for Research on Cancer has reevaluated the evidence for the carcinogenicity of tobacco smoking and tobacco smoke and concluded that there was sufficient evidence in humans that cigarette smoking caused myeloid leukemia and cancer of the nasal cavities and nasal sinus, stomach, liver, kidney (renal-cell carcinoma), and uterine cervix, in addition to the tissue sites mentioned above (IARC 2004).

Cancer Studies in Experimental Animals

Tobacco smoke has been shown to cause cancer in several species of experimental animals. Inhalation exposure to cigarette smoke caused cancer of the larynx in hamsters and increased the incidence of benign and/or malignant lung tumors in rats. In mice exposed to cigarette smoke by inhalation, the increased incidence of lung tumors was not statistically significant; the data for dogs were insufficient for evaluation. Co-exposure of rodents to tobacco smoke and other carcinogens (polycyclic aromatic hydrocarbons or radon daughters) resulted in more respiratory-tract tumors than did exposure to either substance alone. Dermal exposure to cigarette-smoke condensates caused skin tumors in mice and rabbits, and topical application of cigarette-smoke

condensates to the lining of the mouth (oral mucosa) caused lung tumors and lymphoma in mice. Intrapulmonary injection of cigarette-smoke condensate caused lung tumors in rats (IARC 1986, 1987).

Studies on Mechanisms of Carcinogenesis

Individual chemical components of tobacco smoke have been shown to be carcinogenic in humans and experimental animals. Tobacco smoke or tobacco-smoke condensates caused cell transformation, mutations, or other genetic damage in a variety of *in vitro* and *in vivo* assays. The urine of smokers was shown to be mutagenic, and there is evidence that the somatic cells of smokers contain more chromosomal damage than those of nonsmokers (IARC 1986). Lung tumors from smokers contained a higher frequency of mutations in the *p53* tumor-suppressor gene and the *K-ras* proto-oncogene than did tumors from nonsmokers; most of the mutations were G to T transversions (Vineis and Caporaso 1995, IARC 2004).

Properties

Mainstream tobacco smoke is produced at a high temperature (900°C) in the presence of oxygen; it is drawn through the tobacco column and exits through the mouthpiece during puffing. Tobacco pyrolysis products are formed both during smoke inhalation and during the interval between inhalations (NRC 1986). The composition of tobacco smoke is affected by many factors, including the tobacco product, properties of the tobacco blend, chemical additives, smoking pattern, pH, type of paper, filter, and ventilation.

Approximately 4,000 chemicals have been identified in mainstream tobacco smoke, and some researchers have estimated that the actual number may exceed 100,000; however, the currently identified compounds make up more than 95% of the total mass of mainstream smoke. These include carbon oxides, nitrogen oxides, ammonia, hydrogen cyanide, volatile aldehydes and ketones, nonvolatile alkanes and alkenes, benzene, hydrazine, vinyl chloride, isoprenoids, phytochemicals, polynuclear aromatic compounds, alcohols, nonvolatile aldehydes and ketones, phenols, quinones, carboxylic acids, esters, lactones, amines and amides, alkaloids, pyridines, pyrroles, pyrazines, *N*-nitrosamines, metals, radioactive elements, agricultural chemicals, and chemical additives. The nicotine in tobacco is addictive and produces several pharmacological and toxicological effects. Mainstream smoke contains more than 400 individual gaseous components, with nitrogen (58%), carbon dioxide (13%), oxygen (12%), carbon monoxide (3.5%), and hydrogen (0.5%) predominating. Particulates are formed in the range of 0.1 to 1 µm in diameter. Particulate-phase components account for approximately 8% of mainstream smoke, and other vapor-phase components for approximately 5% (IARC 1986, Vineis and Caporaso 1995).

Use

Smoking was introduced to Europe from the Americas in the middle of the 16th century and then spread throughout the world. Currently, the primary source for tobacco smoke is cigarettes. Pipes, cigars, bidis, and other forms are used less frequently (IARC 1986). The use of pipes and cigars was more prevalent in the 18th and 19th centuries, but usage shifted from these products to cigarettes after 1910. Cigarette consumption levels in the United States increased from 2.5 billion in 1900 to 640 billion in 1981, but had declined to 420 billion by 2002 (ALA 2008). In the 2002 National Survey on Drug Use and Health, 30.4% of persons in the United States aged 12 or older reported any tobacco use in the past month; 26.0% reported use of cigarettes, 5.4% use of cigars, and 0.8% use of pipes (SAMHSA 2003).

Production

Tobacco has been an important economic agricultural crop since the 1600s. North and Central America produce the largest quantity. *Nicotiana tabacum* is the most common species of tobacco used in cigarettes, but *N. rustica* also is used in some areas. In the manufacture of smoking tobacco, the tobacco leaf material is manipulated by physical and chemical methods, some of which are intended to reduce the yields of toxic agents and tars in smoke. The tobacco is fine cut and wrapped in paper for consumption. Generally, cigarettes are a blend of various flue-cured grades, burley, Maryland, and oriental tobaccos (IARC 1986). From 1987 to 1997, the annual U.S. tobacco harvest ranged from 1.19 billion pounds to 1.79 billion pounds (USDA 1993, 1998). In 2008, the United States imported over 11 billion cigarettes and exported over 56 billion (USITC 2009).

Exposure

Smokers are exposed primarily by inhalation; however, some exposure may occur through absorption of chemicals present in the tobacco or tobacco smoke directly through the lining of the mouth and gums.

From 1965 to 2001, the estimated number of adult smokers in the United States decreased by 7.8%, to 46.2 million. Over the same period, the percentage of adults who smoked cigarettes declined steadily from 42.4% to 22.6%, for an overall decline of about 47%. In 1991, for the first time in more than 25 years of observation, over half of the adult U.S. population had never smoked or had smoked fewer than 100 cigarettes. Per-capita consumption of cigarettes also has declined; it was 54 in 1900, peaked at 4,345 in 1963, and declined to fewer than 2,000 by 2002. From 1974 to 2001, the percentage of adult smokers who smoked fewer than 15 cigarettes per day increased by 48%, while the percentage of heavy smokers (> 24 cigarettes per day) declined by 42%. The prevalence of smoking cessation increased by over 70% between 1965 and 2001; 44.8 million adults were identified as former smokers in 2001 (ALA 2008). Current strategies in the United States for reducing exposure to tobacco smoke include goals for increasing tobacco-use cessation and reducing the number of new smokers (PHS 2008).

The use of tobacco products varies with gender, age, education, and culture. The prevalence of smoking has always been higher in men than women. In 1965, over half (51.9%) of adult men smoked, compared with 33.9% of women. Smoking prevalence peaked at 67% for men in the 1940s and 1950s and at 44% for women in the 1960s. By 2001, smoking prevalence had declined to 24.9% for men and 20.6% for women. Smoking prevalence was highest in the 25-to-44 age group from 1965 to the mid 1990s. However, smoking increased in the 18-to-24 age group during the 1990s, reaching a peak in 1997, while prevalence continued to decrease in the 25-to-44 age group. Smoking among high-school students increased during the first half of the 1990s, but has since declined. Since 1997, smoking prevalence has been highest in the 18-to-24 age group. As of 2001, smoking prevalence by ethnic group was as follows: 31.5% of Native Americans, 24% of non-Hispanic whites, 22% of non-Hispanic blacks, 16.5% of Hispanics, and 12.5% of Asians (ALA 2008).

Regulations

Executive Order 13058

It is the policy of the executive branch to establish a smoke-free environment for Federal employees and members of the public visiting or using Federal facilities and, therefore, the smoking of tobacco products is prohibited in all interior space owned, rented, or leased by the executive branch of the Federal Government, and in any outdoor areas under executive branch control in front of air intake ducts.

Federal Aviation Administration (FAA)

Smoking is prohibited for all scheduled flights within the United States.

Food and Drug Administration (FDA)

Oral contraceptives must contain a package insert concerning the increased risks associated with tobacco smoking and oral contraceptive use.

Federal Trade Commission (FTC)

All cigarette packages and advertisements for cigarettes must contain a label statement on the risks of smoking.

Advertising of cigarettes on radio and television is banned.

Occupational Safety and Health Administration (OSHA)

OSHA has developed regulations that prohibit cigarette smoking in certain areas.

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Environmental Tobacco Smoke

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Environmental tobacco smoke is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Studies support an association of environmental (passive or secondhand) tobacco smoke with cancer of the lung and, in some cases, the nasal sinus (CEPA 1997). Evidence for an increased cancer risk from environmental tobacco smoke stems from studies examining non-smoking spouses living with individuals who smoke cigarettes, exposure of nonsmokers to environmental tobacco smoke in occupational settings, and exposure to parents' smoking during childhood (IARC 1986, EPA 1992, CEPA 1997). Many epidemiological studies, including large population-based case-control studies, have demonstrated increased risks for developing lung cancer following prolonged exposure to environmental tobacco smoke. A meta-analysis of epidemiological studies found an overall increase in risk of 20% for exposure to environmental tobacco smoke from a spouse who smokes. Increased risk of lung cancer appears to be most strongly related to exposure to environmental tobacco smoke from spousal smoking or exposure in an occupational setting.

Exposure of nonsmokers to environmental tobacco smoke has been demonstrated by detection of nicotine, respirable smoke partic-

ulates, tobacco-specific nitrosamines, and other smoke constituents in the breathing zone, and by measurements of a nicotine metabolite (cotinine) in the urine. However, there is no good biomarker for cumulative past exposure to tobacco smoke, and all of the information collected in epidemiological studies determining past exposure to environmental tobacco smoke relies on estimates that may vary in their accuracy (recall bias). Other suggestions of systematic bias have been made concerning the epidemiological information published on the association of environmental tobacco smoke with cancer. These include misclassification of smokers as nonsmokers; factors related to lifestyle, diet, and other exposures that may be common to couples living together and that may influence lung-cancer incidence; misdiagnosis of cancers that metastasized from other organs to the lung; and the possibility that epidemiological studies examining small populations and showing no effects of environmental tobacco smoke would not be published (publication bias).

Three population-based case-control studies (Brownson *et al.* 1992, Stockwell *et al.* 1992, Fontham *et al.* 1994) and one hospital-based case-control study (Kabat *et al.* 1995) addressed potential systematic biases. Each of the three population-based studies found an increased risk from prolonged exposure to environmental tobacco smoke of a magnitude consistent with previous estimates. The hospital-based study found similarly increased risk, but the results were not statistically significant. The potential for publication bias has been examined and dismissed (CEPA 1997). Some meta-analyses found no increased risk of lung cancer among nonsmokers exposed only in occupational settings; however, when the meta-analyses included only higher-quality studies, an excess risk was found (Wells 1998). Thus, factors related to chance, bias, and/or confounding have been adequately excluded, and exposure to environmental tobacco smoke is established as causally related to human lung cancer.

Since environmental tobacco smoke was listed in the *Ninth Report on Carcinogens*, the International Agency for Research on Cancer has concluded that there is sufficient evidence that involuntary smoking (exposure to secondhand or environmental tobacco smoke) causes lung cancer in humans (IARC 2004).

Studies on Mechanisms of Carcinogenicity

Sidestream smoke and mainstream smoke contain many of the same chemical constituents, including at least 250 chemicals known to be toxic or carcinogenic. As discussed in the profile for Tobacco Smoking (above), exposure to primarily mainstream smoke through active tobacco smoking has been shown to cause cancer of the lung, urinary bladder, renal pelvis, oral cavity, pharynx, larynx, esophagus, lip, and pancreas in humans. Environmental tobacco smoke, sidestream smoke, sidestream smoke condensate, and a mixture of sidestream and mainstream smoke condensate have been shown to cause genetic damage. Increased concentrations of mutagens were found in the urine of humans exposed to environmental tobacco smoke, and lung tumors from nonsmokers exposed to environmental tobacco smoke had mutations in the *p53* tumor-suppressor gene and *K-ras* proto-oncogene similar to those found in lung tumors from smokers (IARC 2004).

Cancer Studies in Experimental Animals

In mice exposed for five months to filtered and unfiltered environmental tobacco smoke (defined as a mixture of 89% sidestream and 11% mainstream smoke) and allowed to recover for four months in filtered air, lung tumor incidence and multiplicity were significantly increased; however, tumor incidence was not significantly increased in mice exposed for five months without a recovery period (Witschi *et al.* 1997a,b). Other studies indicate that inhaled cigarette smoke

and topically applied cigarette-smoke condensate can cause cancer in experimental animals, and that the condensate of sidestream smoke is more carcinogenic to the skin of mice than equivalent amounts (by weight) of mainstream-smoke condensate. Since environmental tobacco smoke was listed in the *Ninth Report on Carcinogens*, IARC (2004) has concluded that there is sufficient evidence in experimental animals for the carcinogenicity of sidestream smoke condensates and limited evidence in experimental animals for the carcinogenicity of mixtures of mainstream and sidestream tobacco smoke.

Properties

Environmental tobacco smoke is a complex mixture of thousands of chemicals that are emitted from burning tobacco. Environmental tobacco smoke is the sum of sidestream smoke, mainstream smoke, compounds that diffuse through the wrapper, and exhaled mainstream smoke. Sidestream smoke contributes at least half of the smoke generated (NRC 1986, CEPA 1997). The composition of tobacco smoke is affected by many factors, as discussed in the profile for Tobacco Smoking (above). Although many of the same compounds are present in both mainstream and sidestream smoke, important differences exist. The ratios of compounds in sidestream and mainstream smoke are highly variable; however, there is less variability in emissions from sidestream smoke than in emissions from mainstream smoke, because smoking patterns and cigarette design have a greater impact on the composition of mainstream smoke (CEPA 1997). Sidestream smoke is generated at lower temperatures than is mainstream smoke (600°C vs. 900°C), is produced in an oxygen-deficient environment, and is rapidly diluted and cooled after leaving the burning tobacco. Mainstream smoke is generated at higher temperatures in the presence of oxygen and is drawn through the tobacco column. These conditions favor formation of smaller particulates in sidestream smoke (0.01 to 0.1 µm in diameter) than in mainstream smoke (0.1 to 1 µm). Sidestream smoke also typically contains higher concentrations of ammonia (40- to 170-fold), nitrogen oxides (4- to 10-fold), and chemical carcinogens (e.g., benzene, 10-fold; *N*-nitrosoamines, 6- to 100 fold; and aniline, 30-fold) than does mainstream smoke (IARC 1986).

A number of chemicals present in environmental tobacco smoke are known or suspected toxicants or irritants with various acute health effects. Prominent among them are the respiratory irritants ammonia, formaldehyde, and sulfur dioxide. Acrolein, hydrogen cyanide, and formaldehyde affect mucociliary function and at higher concentrations can inhibit smoke clearance from lungs (Battista 1976). Nitrogen oxides and phenol are additional toxicants present in environmental tobacco smoke. Over 50 compounds present in environmental tobacco smoke have been identified as *known or reasonably anticipated to be human carcinogens*, including some naturally occurring radionuclides. Most of these compounds are present in the particulate phase (IARC 1986, CEPA 1997).

Use

Environmental tobacco smoke is a by-product of smoking and has no industrial or commercial uses. It is used in scientific research to study its composition and health effects. See the profile for Tobacco Smoking (above) for a brief description of the history and uses of tobacco products.

Production

Environmental tobacco smoke is produced by smoking of various forms of tobacco products. Information on tobacco production is provided in the profile on Tobacco Smoking (above).

Exposure

By 2001, the prevalence of smoking in the United States had declined by about 47% since reaching a peak in the mid 1960s (ALA 2008). Since then, public policies have restricted smoking in buildings and other indoor public places. Nevertheless, environmental tobacco smoke remains an important source of exposure to indoor air contaminants. Based on data from the Third National Health and Nutrition Examination Survey (NHANES III, conducted from 1988 to 1991), 43% of U.S. children aged 2 months to 11 years lived in a home with at least one smoker. In addition, 37% of nonsmoking adults reported exposure to environmental tobacco smoke at home or at work (Pirkle *et al.* 1996). Although levels of cotinine (the primary metabolite of nicotine) in nonsmokers exposed to secondhand smoke fell by 44.7% from 1988 to 2004 (CDC 2010), it has been estimated that 9 million to 12 million children aged six or younger are exposed to environmental tobacco smoke in their homes (EPA 2002).

Because environmental tobacco smoke is a complex mixture, exposure is difficult to measure. Various monitoring methods typically focus on levels of nicotine or respirable suspended particulates in indoor air or cotinine levels in blood, saliva, or urine. Levels of exposure to environmental tobacco have been estimated in many studies as concentrations of respirable suspended particles (particles < 2.5 µm in diameter). The average concentrations of respirable suspended particles in these studies generally ranged from 5 to 500 µg/m³. Concentrations of respirable suspended particles in homes with one or more smokers were 20 to 100 µg/m³ higher than in comparable homes with no smokers (CEPA 1997). Mean nicotine levels in various indoor environments ranged from 0.3 to 30 µg/m³. Typical average concentrations in homes with at least one smoker ranged from 2 to 14 µg/m³.

Nicotine concentrations measured at workplaces from the mid 1970s to 1991 were similar to those measured in homes; however, maximum values were much higher at workplaces (CEPA 1997). Levels of environmental tobacco smoke in restaurants (measured as mean concentrations of respirable suspended particles and nicotine) were 1.6 to 2.0 times the levels in office workplaces and 1.5 times the levels in residences with at least one smoker. Isolating smokers to a specific section of restaurants was found to afford some protection for nonsmokers, but the best protection resulted from seating arrangements that segregated smokers with a wall or partition. However, nonsmokers in restaurants were still exposed to nicotine and respirable particles. Food servers had higher levels of exposure than diners, even if they worked in nonsmoking sections (Lambert *et al.* 1993). Levels of environmental tobacco smoke in bars (based on concentrations of carbon monoxide, nicotine, and respirable suspended particles) were 3.9 to 6.1 times the levels in office workplaces and 4.4 to 4.5 times the levels in residences (Siegel 1993). Nicotine levels as high as 50 to 75 µg/m³ were measured in bars and on airplanes (before smoking was banned). The highest nicotine concentration (1,010 µg/m³) was measured in a car with the ventilation system shut off (CEPA 1997).

NHANES III estimated that 90% of the U.S. population aged 4 years or older had detectable levels of cotinine (Pirkle *et al.* 1996). The median serum cotinine level among nonsmokers was 0.20 ng/mL in 1991, but had decreased by more than 75% to 0.05 ng/mL by 1999 (CDC 2001). An independent nonfederal Task Force on Community Preventive Services, in collaboration with the U.S. Department of Health and Human Services and various public and private partners, recommended various strategies for reducing cigarette smoking and exposure to environmental tobacco smoke (CDC 2000).

Regulations

Executive Order 13058

It is the policy of the executive branch to establish a smoke-free environment for Federal employees and members of the public visiting or using Federal facilities and, therefore, the smoking of tobacco products is prohibited in all interior space owned, rented, or leased by the executive branch of the federal government, and in any outdoor areas under executive branch control in front of air intake ducts.

Federal Aviation Authority (FAA)

Smoking is prohibited on all scheduled flights within the United States.

Guidelines

National Institute for Occupational Safety and Health (NIOSH)

Environmental tobacco smoke is considered a potential occupational carcinogen; exposure should be reduced to the lowest feasible concentration.

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Smokeless Tobacco

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

The oral use of smokeless tobacco is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Smokeless tobacco has been shown to cause cancer of the oral cavity (IARC 1985, 1987, Gross *et al.* 1995). Cancer of the oral cavity has been associated with the use of both chewing tobacco and snuff, which are the two main forms of smokeless tobacco used in the United States. Tumors often arise at the site where the tobacco is placed.

Studies on Mechanisms of Carcinogenicity

Smokeless tobacco products contain nitrosamines that are carcinogenic to animals, including 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosornicotine (NNN), which are listed in the Report on Carcinogens as *reasonably anticipated to be human carcinogens*. The oral use of smokeless tobacco is estimated to be the greatest external source of human exposure to nitrosamines. Nitrosamines are metabolically hydroxylated to form unstable compounds that bind to DNA. Extracts of smokeless tobacco have been shown to cause mutations in bacteria and mutations and chromosomal aberrations in mammalian cells. Furthermore, cells in oral-cavity tissue from smokeless tobacco users have been shown to contain more chromosomal damage than those from nonusers (IARC 1985).

Cancer Studies in Experimental Animals

Evidence for the carcinogenicity of smokeless tobacco in experimental animals is inadequate. Some studies have provided some evidence that snuff or extracts of snuff caused tumors of the oral cavity in rats (Johansson *et al.* 1989); however, most studies had deficiencies in study design. The International Agency for Research on Cancer (IARC 1985, 1987) also concluded that the evidence for the carcinogenicity of smokeless tobacco in experimental animals was inadequate.

Properties

Chewing tobacco consists of the tobacco leaf with the stem removed and various sweeteners and flavorings, such as honey, licorice, or rum. Snuff consists of the entire tobacco leaf (dried and powdered or finely cut), menthol, peppermint oil, camphor, and/or aromatic additives such as attar of roses or oil of cloves (IARC 1985).

Tobacco contains more than 2,500 chemical constituents, including chemicals applied to tobacco during cultivation, harvesting, and processing. The major chemical groups include aliphatic and aromatic hydrocarbons, aldehydes, ketones, alcohols, phenols, ethers, alkaloids, carboxylic acids, esters, anhydrides, lactones, carbohydrates, amines, amides, imides, nitrites, *N*- and *O*-heterocyclic compounds, chlorinated organic compounds, and at least 35 metal compounds. Smokeless tobacco products contain many known or reasonably anticipated human carcinogens, such as volatile and nonvolatile nitrosamines, tobacco-specific *N*-nitrosamines (TSNAs), polynuclear aromatic hydrocarbons, and polonium-210. The concentrations of carcinogenic TSNAs are at least twice those found in other consumer products (Brunnemann *et al.* 1986). TSNAs present in tobacco, including NNK and NNN, are formed from nicotine and other tobacco alkaloids. The concentrations of NNK and NNN, the most carcino-

genic of the TSNAs, are high enough in tobacco that their total estimated doses to long-term snuff users are similar in magnitude to the total doses required to produce cancer in laboratory animals (Hecht and Hoffmann 1989).

Use

Tobacco was widely used by native populations throughout both North and South America by the time the first European explorers arrived in the late 1400s and early 1500s. Over the next few centuries, tobacco use spread to Europe, Africa, China, and Japan. Snuff use was introduced to North American colonists at Jamestown, Virginia, in 1611. Tobacco chewing among American colonists began in the early 1700s, but was not widely accepted until the 1850s (IARC 1985).

Snuff was the most popular form of tobacco in both Europe and the United States before the 1800s. At that time, the finely ground tobacco was primarily sniffed through the nose. The current practice in the United States is to place a small pinch between the lip and gum or cheek and gum (IARC 1985). Moist snuff is the only smokeless tobacco product that has shown increased sales in the United States in recent years. This product is considered the most dangerous form of smokeless tobacco (NCI 1991, USDA 2001). In the three leading brands of snuff, which accounted for 92% of the U.S. market, concentrations of nicotine and TSNAs were significantly higher than in the fourth and fifth most popular brands (Hoffman *et al.* 1995). The highest per-capita consumption of snuff in the United States occurred from 1910 to 1920 at 0.5 lb, but had decreased to 0.15 lb by 1979. After the U.S. Department of Agriculture reclassified several chewing tobacco products as snuff in 1982, the male per-capita consumption of snuff increased to 0.26 lb and remained at 0.2 to 0.3 lb through 2000 (IARC 1985, USDA 2001).

Peak consumption of chewing tobacco in the United States for persons aged 15 years and over was 4.1 lb in 1900; consumption gradually declined to 0.5 lb by 1962. However, per-capita consumption for males aged 18 and over ranged from 1.05 to 1.34 lb between 1966 and 1983 (IARC 1985). Per-capita consumption for males declined to 0.8 lb in 1991, increased to 1.04 lb in 1992, and then declined gradually to 0.9 lb by 2000 (USDA 2001).

Production

Five major U.S. manufacturers of smokeless tobacco products control 99% of the market. The largest company controls over 40% of the total smokeless tobacco market and about 75% of the moist snuff market (FTC 2001).

Annual U.S. production of snuff increased from 1.8 million kilograms (4 million pounds) in 1880 to over 18 million kilograms (40 million pounds) in 1930. Production remained steady through 1950 at 16.4 to 19.9 million kilograms (36 to 44 million pounds) and then declined to 10.9 million kilograms (24 million pounds) by 1980 (IARC 1985). From 1986 to 1999, annual U.S. sales of moist snuff steadily increased from 36 million pounds to over 58 million pounds, while sales of Scotch snuff or dry snuff products declined from 8.1 million pounds to 3.6 million pounds (FTC 2001). In 2008, U.S. imports of snuff and snuff flours were 101,000 kg (222,200 lb), and exports were 619,000 kg (1.4 million pounds) (USITC 2009).

Chewing tobacco products include plug, moist plug, twist/roll, and loose leaf. Total U.S. production declined from 67.4 million kilograms (148.6 million pounds) in 1931 to 29.4 million kilograms (64.8 million pounds) in 1962. Production then rose to 48.1 million kilograms (106.0 million pounds) in 1980, but has since declined steadily. From 1931 to 1980, the market share of plug tobacco declined from 51% to 16%, while the share of loose-leaf tobacco increased from 41% to 68% (IARC 1985). From 1986 to 1999, sales of loose-leaf chewing tobacco

declined from 65.7 million pounds (29.8 million kilograms) to 44.5 million pounds, and sales of plug and twist chewing tobacco combined declined from 8.8 million pounds to 2.8 million pounds (FTC 2001). In 2008, the United States imported 146,000 kg (321,000 lb) of chewing tobacco and exported 147,000 kg (323,000 lb) (USITC 2009).

Exposure

Individuals who use smokeless tobacco are exposed primarily by absorption through the oral or nasal mucosa and by ingestion. Occupational exposure to tobacco may occur through skin contact, inhalation of dust, and ingestion of dust during processing and manufacturing. Many smokeless tobacco users are exposed during most of their working hours, and some use these products 24 hours per day (IARC 1985).

Consumption of smokeless tobacco products showed a resurgence in the late 1970s, after decades of decline. Increased use of these products was particularly dramatic among adolescent boys, increasing by 250% or more between 1970 and 1985 (NCI 1991). The estimated number of smokeless tobacco users in the early 1980s ranged from 7 million to 22 million (IARC 1985). In 1991, 2.9% of adults aged 18 and over used smokeless tobacco, including an estimated 4.8 million men and 0.53 million women. About 67% of snuff users and 45% of chewing-tobacco users reported daily use. The prevalence of use was highest (8.2%) in men aged 18 to 24 (CDC 1993). In 17 states surveyed in 1997, the percentage of users aged 18 and over ranged from approximately 1.4% to 8.8%; use was much higher among men (2.6% to 18.4%) than women (0 to 1.7%) (CDC 1998). In 2001, it was estimated that there were 10 million U.S. users of smokeless tobacco, including 3 million under the age of 21 (UMN 2001).

Regulations

Federal Trade Commission (FTC)

All smokeless tobacco products and advertisements for smokeless tobacco must contain a label statement on the risks of smokeless tobacco.

Advertising of smokeless tobacco products on radio and television is banned.

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Toluene Diisocyanates

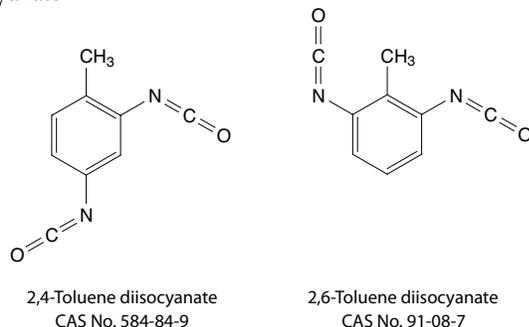
CAS No. 26471-62-5

Reasonably anticipated to be a human carcinogen

First listed in the *Fourth Annual Report on Carcinogens* (1985)

Also known as TDI; 1,3-diisocyanatomethyl benzene; isocyanic acid, methyl-*m*-phenylene ester; or tolylene diisocyanate

Isomers also known as toluene-2,4-diisocyanate and toluene-2,6-diisocyanate



Carcinogenicity

Toluene diisocyanates are *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to toluene diisocyanates caused tumors at several different tissue sites in rats and mice. Administration of commercial-grade toluene diisocyanate (analyzed as 85% 2,4 isomer and 15% 2,6 isomer) by stomach tube caused liver tumors (hepatocellular adenoma) in female rats and mice, benign mammary-gland tumors (fibroadenoma) in female rats, and benign tumors of the pancreas (acinar-cell adenoma) in male rats. It also increased the combined incidences of benign and malignant tumors of subcutaneous tissue (fibroma and fibrosarcoma) in male rats and of the blood vessels (hemangioma and hemangiosarcoma) in female mice (NTP 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to toluene diisocyanates.

Properties

Toluene diisocyanates exist at room temperature as a clear, colorless to pale-yellow liquid with a pungent odor. They decompose in water, but are very soluble in acetone and benzene, and are miscible with ether, diglycol monomethyl ether, carbon tetrachloride, chlorobenzene, kerosene, and olive oil. They are combustible when exposed to heat or flame and darken when exposed to sunlight (IARC 1999, HSDB 2009). 2,4-Toluene diisocyanate is available as a commercial product with purity of at least 99.5%, but most commonly as an 80:20 mixture of 2,4-toluene diisocyanate and 2,6-toluene diisocyanate (IARC 1986). Physical and chemical properties of toluene diisocyanates are listed in the following table.

Property	Toluene diisocyanates mixed	2,4-Toluene diisocyanate	2,6-Toluene diisocyanate
Molecular weight ^a	174.2	174.2	174.2
Specific gravity at 25°C ^a (g/mL)	1.22 or 0.01	1.22 or 0.01	1.22 or 0.01
Melting point ^a	11°C to 14°C (FP)	19.5°C to 21.5°C	18.3°C
Boiling point ^a	251°C	251°C	129°C to 133°C at 18 mm Hg
Log K_{ow} ^b	3.74	3.74	3.74
Water solubility at 25°C ^b	0.0376 g/L	0.0376 g/L	decomposes
Vapor pressure ^a	2.30×10^{-2} mm Hg at 25°C	8.0×10^{-3} mm Hg at 20°C	2.1×10^{-2} mm Hg at 25°C
Vapor density relative to air ^c	6	6	6

Sources: ^aHSDB 2009, ^bChemIDplus 2009, ^cAkron 2009. FP = freezing point.

Use

Toluene diisocyanates are used primarily to manufacture flexible polyurethane foams for use in furniture, bedding, and automotive and airline seats. Other, smaller uses are for polyurethane elastomers (for automobile bumper covers, industrial rollers, sport soles and boots, and mechanical goods) and coatings (for automotive refinishing, wood finishes, and high-performance anti-corrosion coatings) (ICIS 2009). Toluene diisocyanate-based rigid polyurethane foam is used in household refrigerators and for residential sheathing or commercial roofing in board or laminate form (IARC 1986). "Pour-in-place" or "spray-in" rigid foam is used as insulation for truck trailers, railroad freight cars, and cargo containers. Polyurethane-modified alkyds contain approximately 6% to 7% isocyanate, mostly toluene diisocyanates, and are used as coating materials, such as floor finishes, wood finishes, and paints. Moisture-curing coatings are used as wood and concrete sealants and floor finishes. Aircraft, truck, and passenger-car coatings often are composed of toluene diisocyanate prepolymer systems. Castable urethane elastomers are used in applications requiring strength, flexibility, and shock absorption, and are resistant to oil, solvents, and ultraviolet radiation. They are used in adhesive and sealant compounds and in automobile parts, shoe soles, rollerskate wheels, pond liners, and blood bags. They are also used in oil fields and mines. Certain elastomer products are produced from the pure 2,4 isomer rather than the 80:20 mixture.

Production

Toluene diisocyanates have been produced commercially since the late 1930s (IARC 1986). In 1993, the production capacity for toluene diisocyanates in North America was estimated at more than 1 billion pounds (IARC 1999). In 2009, the United States had one producer of each isomer of toluene diisocyanate (2,4 and 2,6), three producers of the mixed isomer product (SRI 2009), one supplier of mixed toluene diisocyanates, three suppliers of 2,6-toluene diisocyanate, and fourteen suppliers of 2,4-toluene diisocyanate (ChemSources 2009).

Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of an 80:20 mixture of 2,4- and 2,6-toluene diisocyanate totaled 100 million to 500 million pounds in 1986, 500 million to 1 billion pounds from 1990 to 2002, and over 1 billion pounds in 2006 (EPA 2004, EPA 2009). The reported quantities of 2,4-toluene diisocyanate were 100 million to 500 million pounds in 1986 and 1990, falling to between 1 million and 10 million pounds from 1994 to 2002. Reported quantities of 2,6-toluene diisocyanate were 50 million to 100 million pounds in 1986 and 10 million to 50 million pounds in 1990; no inventory update reports for 2,6-toluene diisocyanate have been filed since 1990 (EPA 2004).

U.S. imports of mixed isomers of toluene diisocyanate were 984,000 kg (2.1 million pounds) in 1989, reaching a low of 1,000 kg (2,200 lb) in 1996 and a peak of 15 million kilograms (32 million pounds) in 2006; 2008 imports were 500,000 kg (1.1 million pounds) (USITC 2009). U.S. imports of unmixed isomers were 426,000 kg (939,000 lb) in 1989, reaching a low of 9,000 kg (19,800 lb) in 1998 and a peak of 1.3 million kilograms (2.8 million pounds) in 2004; 2008 imports were 130,000 kg (286,000 lb) in 2008. U.S. exports of mixed isomers of toluene diisocyanate were 62 million kilograms (125 million pounds) in 1989, rising to a high of 277 million kilograms (609 million pounds) in 2003; they have since trended lower. U.S. exports of unmixed isomers of toluene diisocyanate peaked in 1994 at 46 million kilograms (101 million pounds), falling to a low of 3.9 million kilograms (8.6 million pounds) in 2008.

Exposure

The primary routes of potential human exposure to toluene diisocyanates are inhalation and dermal contact. Exposure to toluene diisocyanates is primarily occupational; however, several commercially available household products may pose a risk of exposure to toluene diisocyanates to the general population if used indiscriminately. For example, consumers may be exposed to toluene diisocyanates volatilized from polyurethane varnishes during the application of such coatings (IPCS 1987). A model developed to predict the background concentration of toluene diisocyanate in Western Europe estimated that if annual toluene diisocyanate usage were 100,000 tons, the background air concentration would be approximately 0.0001 $\mu\text{g}/\text{m}^3$ (Tury *et al.* 2003).

According to EPA's Toxics Release Inventory, environmental releases of mixed toluene diisocyanates were highest in 2001 and 2004, at over 125,000 lb; 45,642 lb was released in 2003. The same trend held for the individual isomers; however, releases were lowest in 1995 for 2,4-toluene diisocyanate and in 2002 for 2,6-toluene diisocyanate. In 2006, releases of toluene diisocyanates (mixed isomers), 2,4-toluene diisocyanate, and 2,6-toluene diisocyanate from 139 facilities totaled 73,778 lb (TRI 2009).

Because of the high volatility of toluene diisocyanates, exposure can occur in all phases of its manufacture and use (IPCS 1987). Toluene diisocyanate occurs in the work environment, primarily in air, during its commercial production, handling, and processing and during the production of polyurethane foam and coated fabrics. However, manual handlers of uncured polyurethane foam were significantly more likely to have detectable urinary adducts of toluene diisocyanates than non-handlers working in areas with similar air concentrations of toluene diisocyanate (Austin 2007). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that nearly 40,000 workers potentially were exposed to toluene diisocyanates (NIOSH 1990). Workers potentially exposed to toluene diisocyanates include adhesive workers, insulation workers, diisocyanate-resin workers, lacquer workers, organic-chemical synthesizers, paint sprayers, polyurethane makers, rubber workers, ship builders, textile processors, and wire-coating workers (IPCS 1987). Worker exposure to toluene diisocyanates is most likely to occur during sample collection, residue removal, spill clean-up, and equipment maintenance; employees are required to use air-line respirators during these operations. The highest exposure levels have occurred during the spray application of polyurethane foam. The construction industry uses polyurethane formulations in thermal insulation, adhesives, lacquers, and paints. In most cases, the foam is applied through air-spraying in confined spaces; exposure to concentrations above safe limits are a particular concern for the sprayers and their helpers. In the United States, a typical modern housing unit of 1,800 ft^2 floor

space, including furniture, carpet underlay, and bedding, contains 306 lb of flexible polyurethane foam. The transportation industry uses approximately 21% of flexible polyurethane foam for automobile seating and padding, resulting in the use of 24 to 31 lb of polyurethane per automobile (IARC 1986).

Studies summarized by the International Agency for Research on Cancer (IARC 1986, 1999) reported workplace air concentrations of toluene diisocyanates ranging from less than 1 to more than 1,000 $\mu\text{g}/\text{m}^3$; the current Occupational Safety and Health Administration ceiling concentration is 0.02 ppm ($\sim 140 \mu\text{g}/\text{m}^3$). Workplace air concentrations measured in 2005 close to the mixer in a polyurethane factory were up to 12.1 $\mu\text{g}/\text{m}^3$ for 2,4-toluene diisocyanate, 8.1 $\mu\text{g}/\text{m}^3$ for 2,6-toluene diisocyanate, and 20.2 $\mu\text{g}/\text{m}^3$ for total toluene diisocyanates (Tinnerberg and Mattsson 2008). Analysis of the isomeric composition of atmospheric toluene diisocyanates in a plant producing polyurethane foam found a higher concentration of the 2,6 isomer than of the 2,4 isomer, particularly at the finishing end of the production process. Median air concentrations of 2,4-toluene diisocyanate were 5.0 $\mu\text{g}/\text{m}^3$ for initial mixing and 2.3 $\mu\text{g}/\text{m}^3$ for finishing. The respective median concentrations for the 2,6 isomer were 6.4 and 7.8 $\mu\text{g}/\text{m}^3$, with a maximum exceeding 450 $\mu\text{g}/\text{m}^3$ at the finishing end. These findings were attributed to enhanced emission of the less chemically active 2,6 isomer from the cured foam bats and retention of the 2,4 isomer as a polymer. Aniline and the 2,4 and 2,6 isomers of toluene diisocyanate were detected under controlled experimental conditions in the thermodegradation fumes of polyurethane varnish used in the insulation of copper wire. Consistent with these findings, the compounds were also detected in the workplace atmosphere during the industrial production of polyurethane-coated wire (IARC 1986, 1999).

Since 2001, exposure has been confirmed by measuring toluene diisocyanate adducts in the plasma and urine of exposed workers. Toluenediamine, a metabolite of toluene diisocyanate, has been measured in the plasma at levels up to 27.2 ng/mL for 2,4-toluenediamine and 62.1 ng/mL for 2,6-toluenediamine (Tinnerberg and Mattsson 2008). Swedish workers manufacturing polyurethane products excreted 53.2 to 259.6 nmol of toluenediamine per gram of creatinine (Bolognesi *et al.* 2001). Concentrations of toluene diisocyanate in urine of occupationally exposed workers ranged from 0 to 76 $\mu\text{g}/\text{L}$ for the 2,4 isomer and from 0 to 31 $\mu\text{g}/\text{L}$ for the 2,6 isomer.

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for the safe transport of toluene diisocyanate on ships and barges.

Department of Transportation (DOT)

Toluene diisocyanate is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: 2,4-Toluene diisocyanate is listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of diisocyanates is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: 2,4-Toluene diisocyanate is subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of toluene diisocyanates = U223, K027.

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Ceiling concentration = 0.02 ppm (0.14 mg/m³) for toluene-2,4-diisocyanate.

Guidelines**National Institute for Occupational Safety and Health (NIOSH)**

Immediately dangerous to life and health (IDLH) limit = 2.5 ppm for toluene-2,4-diisocyanate. Toluene-2,4-diisocyanate is listed as a potential occupational carcinogen.

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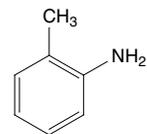
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o*-Toluidine and Its Hydrochloride*CAS Nos. 95-53-4 and 636-21-5**

Reasonably anticipated to be human carcinogens

o-Toluidine was first listed in the *Third Annual Report on Carcinogens* (1983)

o-Toluidine hydrochloride was first listed in the *Second Annual Report on Carcinogens* (1981)

**Carcinogenicity**

o-Toluidine and *o*-toluidine hydrochloride are reasonably anticipated to be human carcinogens based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to *o*-toluidine hydrochloride caused tumors at several different tissue sites in rats and mice. In rats, it caused cancer of the connective tissue (several types of sarcoma) in the spleen and other organs in both sexes; benign and malignant tumors of the urinary bladder (transitional-cell papilloma and carcinoma) and mammary gland (adenoma and fibroadenoma) in females; and mesothelioma of the abdominal cavity and the scrotum and benign and malignant tumors of the subcutaneous tissue (mainly fibroma) in males. In mice, it caused blood-vessel tumors (hemangioma and hemangiosarcoma) in both sexes and benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in females (IARC 1982).

Cancer Studies in Humans

The human cancer studies available when *o*-toluidine was evaluated for listing in the *Third Annual Report on Carcinogens* were primarily case reports of urinary-bladder cancer occurring among workers exposed to dyes in addition to *o*-toluidine. These studies were inadequate for evaluating effects specifically from exposure to *o*-toluidine (IARC 1978, 1982). Since then, additional studies in humans have been identified. The International Agency for Research on Cancer classified *o*-toluidine as carcinogenic to humans based on cohort studies of workers exposed to *o*-toluidine that reported increased risk of urinary-bladder cancer (Baan *et al.* 2008).

Properties

o-Toluidine is an aromatic amine that exists at room temperature as a light-yellow liquid that darkens to reddish brown upon exposure to air (IPCS 1998, Akron 2009). It has an aromatic aniline-type odor. *o*-Toluidine is slightly soluble in water, soluble in alcohol, ether, and dilute acids, and miscible in carbon tetrachloride (HSDB 2009). *o*-Toluidine hydrochloride is the hydrochloride salt of this aromatic amine. It is a green or white crystalline solid at room temperature (Akron 2009). It is very soluble in water, soluble in alcohol, and insoluble in ether and benzene (HSDB 2009). It is sensitive to exposure to moisture and light (IARC 2000). Physical and chemical properties of *o*-toluidine and its hydrochloride are listed in the following table.

Property	o-Toluidine	o-Toluidine hydrochloride
Molecular weight	107.2 ^a	143.6 ^a
Specific gravity	1.008 at 20°C ^a	NR
Melting point	-16.3°C ^a	215°C ^a
Boiling point	200.3°C ^a	242.2°C ^a
Log K_{ow}	1.32 ^a	1.62 ^b
Water solubility	16.6 g/L at 25°C ^a	8290 mg/L at 25°C ^b
Vapor pressure	0.260 mm Hg at 25°C ^b	0.293 mm Hg at 25°C ^b
Vapor density relative to air	3.69 ^a	NR
Dissociation constant (p <i>K</i> _a)	4.44 at 25°C ^a	4.39 at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009. NR = not reported.

Use

o-Toluidine and o-toluidine hydrochloride are used primarily as intermediates in the manufacture of more than 90 dyes and pigments (NCI 1979, IARC 1982, 2000). They are used in acid-fast dyestuffs, azo pigments and dyes, triarylmethane dyes, sulfur dyes, and indigo compounds and as a photographic dye. o-Toluidine is also used as an intermediate for synthetic rubber and rubber vulcanizing chemicals, pharmaceuticals, and pesticides and as a curing agent in epoxy resin systems. Other minor uses of o-toluidine and its hydrochloride salt are as an intermediate in organic synthesis and as an ingredient in a clinical laboratory reagent for glucose and hemoglobin analyses.

Production

In the United States, commercial production was first reported for o-toluidine in 1956 and for o-toluidine hydrochloride in 1922 (IARC 1982, 2000). Annual production of o-toluidine was estimated at 500,000 kilograms to 5 million kilograms (1.1 million to 11 million pounds) in the late 1970s, increasing to 6.6 million to 12.8 million kilograms (14.5 million to 28.2 million pounds) by the early 1990s (IARC 2000). In 2009, o-toluidine was manufactured by 18 companies worldwide, including 3 in the United States (SRI 2009), and was available from 18 U.S. suppliers (ChemSources 2009). o-Toluidine hydrochloride has not been commercially produced in the United States since 1975 (HSDB 2009); however, it was available from six U.S. suppliers in 2009 (ChemSources 2009). In 2008, U.S. imports of "toluidines and their derivatives, salts thereof" and "other toluidines and their derivatives, and salts thereof" totaled 33.8 million pounds (USITC 2009). No import volumes were reported for this category before 2003. U.S. exports for this category have been reported for every year since 1989; volumes ranged from a high of 21.6 million pounds in 1992 to a low of 3.9 million pounds in 2002. Reports filed from 1986 through 2002 under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of o-toluidine totaled 10 million to 50 million pounds (EPA 2004).

Exposure

The potential routes of exposure to o-toluidine and its hydrochloride salt are inhalation, dermal contact, and ingestion (HSDB 2009). o-Toluidine is a metabolite of prilocaine, a topical anesthetic. The general population may be exposed to low concentrations of o-toluidine in indoor and outdoor ambient air, tobacco smoke, or food, or by dermal contact with commercial products. Consumers may possibly be exposed to o-toluidine from residues present in commercial dyes used on textiles (IARC 2000). o-Toluidine has been detected in blood and breast milk (Gazarian *et al.* 1995) and was measured in the urine of individuals with no known exposure at a median concentration of 0.12 µg/L (Weiss and Angerer 2002). o-Toluidine is present in cigarette smoke at a concentration of up to 144 ng per cigarette (Stabbert *et al.* 2003). It has been measured in the urine of smokers at a mean

concentration of 117 ng/L and in the urine of nonsmokers at 55 ng/L (Riedel *et al.* 2006). Hemoglobin (Hb) adducts of o-toluidine were measured in children at three locations in Germany who were either exposed or not exposed to environmental tobacco smoke (Richter *et al.* 2001). The first two locations were urban, and all children showed high levels of o-toluidine adducts, with no significant differences between the exposed and unexposed groups (Munich: 642 pg/g of Hb exposed, 620 pg/g unexposed; Augsburg: 574 pg/g exposed, 621 pg/g unexposed). At the third location, which was rural, all children had much lower levels of o-toluidine adducts, and levels differed significantly between the exposed and unexposed groups (376 pg/g of Hb exposed, 558 pg/g unexposed).

According to EPA's Toxics Release Inventory, environmental releases of o-toluidine between 1988 and 2009 ranged from 10,800 to 55,000 lb, while releases of o-toluidine hydrochloride ranged from 0 to 265 lb. In 2007, 16,348 lb of o-toluidine was released from 12 facilities, and 10 lb of o-toluidine hydrochloride was released from one facility (TRI 2009). o-Toluidine has been detected in effluents from refineries and production facilities and in river water, process water, and groundwater (IARC 2000). In 1979, it was measured in the Rhine River at concentrations of 0.03 to 1.8 µg/L and in Japan at concentrations of up to 20 µg/L (IPCS 1998).

Occupational exposure to o-toluidine or o-toluidine hydrochloride is most likely to occur through inhalation and dermal contact (Korinath *et al.* 2006). o-Toluidine has been measured in personal air samples and urine from automobile workers involved in rubber vulcanization, at concentrations ranging from 26.63 to 93.93 µg/m³ in air and 54.65 to 242.88 µg/L in urine. The higher urine concentrations were measured in workers with impaired skin (Korinath *et al.* 2007). In another study of these workers, workplace ambient air concentrations of o-toluidine were 11.0 µg/m³ for smokers and 61.4 µg/m³ for nonsmokers, and urine concentrations were 14.5 µg/L for smokers and 38.6 µg/L for nonsmokers. It also appeared that skin-barrier creams recommended for use on the hands of workers had a negative effect, increasing the transfer of o-toluidine across the skin barrier. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 30,000 workers, including 15,500 women, potentially were exposed to o-toluidine. The potential for exposure was greatest among dye and pigment makers (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of o-toluidine on ships and barges.

Department of Transportation (DOT)

Toluidines are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: o-Toluidine is listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb for o-toluidine and o-toluidine hydrochloride.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: o-Toluidine is a listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of o-toluidine or o-toluidine hydrochloride = U222, U328, K112, K113, K114.

Listed as hazardous constituents of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 5 ppm (22 mg/m³) for o-toluidine.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 2 ppm for o-toluidine.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 50 ppm for o-toluidine.

o-Toluidine is listed as a potential occupational carcinogen.

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Toxaphene

CAS No. 8001-35-2

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Carcinogenicity

Toxaphene is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dietary exposure to toxaphene caused tumors in two rodent species and at two different tissue sites. In mice of both sexes, it increased the combined incidence of benign and malignant liver tumors (hepatocellular adenoma and carcinoma), and in rats of both sexes, it caused benign tumors of the thyroid gland (follicular-cell adenoma) (IARC 1979, 2001, NCI 1979).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to toxaphene. Since toxaphene was listed in the *Second Annual Report on Carcinogens*, additional epidemiological studies have been identified. Two case-control studies, one for non-Hodgkin's lymphoma and one for leukemia, found no association with toxaphene exposure (IARC 2001).

Properties

Toxaphene is a manufactured insecticide containing a complex mixture of at least 670 chemicals, including chlorobornanes, chlorocamphenes, and other bicyclic chloroorganic compounds (ATSDR 1996). The relative proportions of the major components of the pesticide are essentially the same in different formulations. Toxaphene exists at room temperature as a yellow-to-amber waxy solid with a pleasant, piney odor (HSDB 2010). It is practically insoluble in water but is freely soluble in aromatic hydrocarbons, such as benzene and xylene, and is readily soluble in aliphatic organic solvents, such as carbon tetrachloride, ethylene dichloride, kerosene, or mineral oil (ATSDR 1996). Toxaphene is stable under normal room temperatures and pressures (Akron 2010). Physical and chemical properties of toxaphene are listed in the following table.

Property	Information
Molecular weight	414 (average) ^a
Specific gravity	1.65 at 25°C ^a
Melting point	65°C to 90°C ^a
Boiling point	decomposes ^a
Log K _{ow}	5.9 (median) ^b
Water solubility	0.00055 g/L at 20°C ^a
Vapor pressure	6.69 × 10 ⁻⁶ mm Hg at 20°C ^b
Vapor density relative to air	14.3 ^a

Sources: ^aHSDB 2010, ^bChemIDplus 2010.

Use

Toxaphene was used primarily as an insecticide for cotton; therefore, most of it was used in the southern United States from Texas to Georgia (HSDB 2010). It was also used to a lesser extent on other crops (e.g., corn, small grains, fruits, vegetables, and soybeans), to control ectoparasites (e.g., lice, flies, ticks, mange, and scab mites) on livestock, and to kill undesirable fish species in lakes and streams (ATSDR 1996). Use of toxaphene in the United States has been re-

corded since 1966 (HSDB 2010); during the early to mid 1970s, toxaphene became the most heavily used pesticide in the United States. The U.S. Environmental Protection Agency cancelled most of the pesticide registrations for toxaphene in 1982, and all uses were banned in 1990 (ATSDR 1996). After 1982, existing stocks of toxaphene could be used only in selected markets or on a case-by-case emergency basis as determined by EPA, and after 1990, remaining stocks could not be sold or used in the United States.

Annual use of toxaphene in the United States was over 34 million pounds from 1966 to 1976 (HSDB 2010), declining to 6.6 million pounds in 1982. By 1989, toxaphene was no longer used in the United States. During the peak years, approximately 85% of all toxaphene was used on cotton, 7% was used to control insect pests on livestock and poultry, 5% was used on other field crops, 3% was used on soybeans, and less than 1% was used on sorghum (IARC 1979). Toxaphene use continues in some countries, and it may be manufactured in the United States for export to those countries (ATSDR 1996). Cumulative global usage of toxaphene was interpolated to be 670 million kilograms (1.5 billion pounds) between 1970 and 1995 (Voldner and Li 1995).

Production

Commercial production of toxaphene in the United States began in 1947, and four U.S. companies have produced toxaphene commercially (IARC 1979, ATSDR 1996, HSDB 2010). Technical toxaphene can be produced commercially by reacting chlorine gas with technical camphene in the presence of ultraviolet radiation and catalysts, yielding chlorinated camphene containing 67% to 69% chlorine by weight. Between 1964 and 1982, an estimated 234,000 metric tons (over 500 million pounds) of toxaphene was produced in the United States (HSDB 2010). Between 25% and 35% of the annual production was exported. Production peaked in 1975 at 59.4 million pounds, declining more than 90% by 1982 (ATSDR 1996). In 2010, toxaphene was available from 11 suppliers worldwide, including 7 U.S. suppliers (Chem Sources 2010).

It also appears that some polychlorinated camphenes like toxaphene may be generated unintentionally by other manufacturing processes that include chlorination, for example, in the pulp and paper industry (ATSDR 1996).

Exposure

The routes of potential human exposure to toxaphene are ingestion, dermal contact, and inhalation (HSDB 2010). Toxaphene was the most widely used pesticide in the United States in the 1970s (Bidleman *et al.* 1998). Because toxaphene is no longer used in the United States, current exposure is due mainly to its persistence of the environment (ATSDR 1996).

The U.S. Food and Drug Administration estimated the average daily intake of toxaphene at 0.003 µg/kg of body weight from 1986 to 1991 and 0.007 to 0.02 µg/kg from 1986 to 1991. The highest estimated intakes were for children aged 2 years. In other studies conducted between 1981 and 1986, toxaphene was detected in fewer than half of 14,492 samples of foods either domestically produced or imported from 79 countries, but less than 1% of those samples contained toxaphene at levels exceeding regulatory limits (HSDB 2010). In the FDA Total Diet Study, conducted from 1991–93 through 2003–04, toxaphene was detected in 14 foods. It was found most frequently and at the highest mean concentrations in peanut butter (0.02018 ppm) and dry-roasted peanuts (0.02609 ppm) (FDA 2003). Specific toxaphene congeners have been measured in pooled human serum from three cities in the United States: Atlanta, Georgia, Chicago, Illinois, and Cincinnati, Ohio (Barr *et al.* 2004). In northernmost Canada, toxaphene levels in maternal and cord blood plasma were highest among the Inuit population who consumed marine mammals as a part of their regular diet (Butler Walker *et al.* 2003).

According to EPA's Toxics Release Inventory, environmental releases of toxaphene from 1990 to 2007 ranged from zero to a high of 25,602 lb in 1998. From 2000 to 2007, releases ranged from a high of 6,787 lb in 2005 to a low of 1,217 lb in 2007. In 2008, 11 facilities released a total of 418,525 lb of toxaphene, nearly all of which (415,473 lb) was released to an on-site hazardous-waste landfill by a single facility (TRI 2010). Toxaphene is persistent in soil; in one study, 45% of the toxaphene applied to a sandy loam soil in 1951 was still present 20 years later (IARC 1979). The mean concentration of toxaphene in soil in in 1999–2000 was 688 ng/g of dry soil in Alabama, Louisiana, and Texas and 2,500 ng/g in South Carolina (Kannan *et al.* 2003, Bidleman and Leone 2004). Toxaphene is biotransformed under anaerobic conditions in soil and sediment, with a half-life in the range of weeks or months. Under aerobic conditions, its half-life is in the range of years. Toxaphene bioaccumulates in the environment and is biomagnified through the aquatic food chain.

In the 1990s, toxaphene was found to be widely distributed throughout the atmosphere as a result of air dispersion and deposition (Alegria *et al.* 2006). In 1994–95, the air concentration of toxaphene in Columbia, South Carolina, was much lower than it had been in 1977 to 1985, but much higher than near the Great Lakes (Bidleman *et al.* 1998). Toxaphene was measured in precipitation over Lake Ontario from 1994 to 1998, indicating loading of toxaphene to the lake by wet deposition (Burniston *et al.* 2005). In 2000, it was estimated that 15 million kilograms (33 million pounds) of toxaphene was still present in North American air, water, and soil (MacLeod *et al.* 2002) and that over 25% of the remaining toxaphene had moved through long-range atmospheric transport to the Great Lakes region. A systematic air-sampling study conducted in 2002–03 supported the premise that most toxaphene in the atmosphere in the northern United States had volatilized from southern cotton fields, where it had been heavily applied before 1982, and had been transported in the atmosphere to Indiana and the upper Great Lakes (James and Hites 2002, Jantunen and Bidleman 2003, Hoh and Hites 2004).

Toxaphene was measured in fish in the Great Lakes and in Lake Tahoe; the highest concentrations were found in lake trout (a species with high lipid content) in Lake Superior (Andrews *et al.* 1993, Datta *et al.* 1999, Carlson and Swackhamer 2006). Toxaphene was also found in other locations and in other species, including farm-raised and wild salmon. Fish in subarctic lakes were found to contain toxaphene at levels of concern for human health (Kidd *et al.* 1995). Toxaphene was also detected in fish from Alaska's Yukon River Basin (Hinck *et al.* 2006) and in marine mammals in the Alaskan Arctic at levels similar to those found in Northern Canada and Greenland. The native Arctic Alaskan population thus may be exposed to toxaphene through subsistence consumption of marine mammals (Becker *et al.* 1997, Becker 2000, Hoekstra *et al.* 2002).

In the past, the risk of occupational exposure to toxaphene was greatest for manufacturers of toxaphene, cotton farmers, and pesticide applicators (HSDB 2010). No estimates are available of the number of people potentially exposed through past agricultural use and handling, but the number may be substantial, because of toxaphene's importance as an agricultural pesticide in the 1970s (ATSDR 1996).

In the past, the risk of occupational exposure to toxaphene was greatest for manufacturers of toxaphene, cotton farmers, and pesticide applicators (HSDB 2010). No estimates are available of the number of people potentially exposed through past agricultural use and handling, but the number may be substantial, because of toxaphene's importance as an agricultural pesticide in the 1970s (ATSDR 1996).

Regulations

Department of Transportation (DOT)

Toxaphene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)**Clean Air Act**

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Designated a hazardous substance.

Water Quality Criteria: Based on fish or shellfish and water consumption = 0.00028 µg/L; based on fish or shellfish consumption only = 0.00028 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Reportable quantity (RQ) = 1 lb.

Threshold planning quantity (TPQ) = 500 lb for the solid in powder form of particle size < 100 µm or in solution or molten form; = 10,000 lb for all other forms.

Federal Insecticide, Fungicide, and Rodenticide Act

Registrations for all uses of toxaphene have been canceled.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of toxaphene = P123, K041, K098.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.003 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.003 mg/L.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 0.5 mg/m³.

Guidelines**American Conference of Governmental Industrial Hygienists (ACGIH)**

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m³.

Threshold limit value – short-term exposure limit (TLV-STEL) = 1 mg/m³.

National Institute for Occupational Safety and Health (NIOSH)

Immediately dangerous to life and health (IDLH) limit = 200 mg/m³.

Listed as a potential occupational carcinogen.

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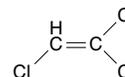
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Trichloroethylene**CAS No. 79-01-6**

Reasonably anticipated to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Also known as 1,1,2-trichloroethene or TCE

**Carcinogenicity**

Trichloroethylene is reasonably anticipated to be a human carcinogen based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and information from studies on mechanisms of carcinogenesis.

Cancer Studies in Humans

Evidence for the carcinogenicity of trichloroethylene in humans comes from seven cohort studies with specific trichloroethylene exposure well characterized for individual study subjects. A meta-analysis of these cohort studies found that occupational exposure to trichloroethylene was associated with excess incidences of liver cancer,

kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma, with the strongest evidence for the first three types of cancer. Elevated risks of death from Hodgkin's disease, multiple myeloma, cervical cancer, and liver cancer also were observed. Nevertheless, these studies are based on a relatively small number of exposed workers and were confounded by exposure to other solvents and other cancer risk factors. Findings from other cohort studies, with less accurate assessment of trichloroethylene exposure, were more variable. In case-control studies, exposure to trichloroethylene was assessed less accurately; in many studies, it was estimated from exposure to solvents in general. These studies typically reported higher cancer rates for tissue sites similar to those observed in the cohort studies. Elevated risks were most consistently observed for kidney cancer, liver cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and cervical cancer (Wartenberg *et al.* 2000).

Cancer Studies in Experimental Animals

Trichloroethylene caused tumors in mice and rats at several different tissue sites by two different routes of exposure. In mice, exposure to trichloroethylene by inhalation or by stomach tube caused benign and malignant liver tumors (hepatocellular adenoma and carcinoma) in both sexes (NCI 1976, Maltoni *et al.* 1988, NTP 1990, IARC 1995); inhalation exposure also caused lung tumors in both sexes and lymphoma in females (Henschler *et al.* 1980, IARC 1995). In rats, exposure to trichloroethylene by inhalation or by stomach tube caused kidney cancer (tubular adenocarcinoma) and testicular tumors (interstitial-cell tumors) in males (Maltoni *et al.* 1988, NTP 1988, 1990); leukemia also was observed in males whose survival was reduced after exposure by stomach tube (Maltoni *et al.* 1988).

Studies on Mechanisms of Carcinogenesis

Trichloroethylene is rapidly absorbed from the stomach, intestines, and lungs (IARC 1976, 1979, 1995, NTP 2000). It is distributed throughout the body and concentrates in fatty tissues, such as the liver, brain, and body fat. Trichloroethylene is metabolized primarily through oxidation by cytochrome P450 and conjugation with glutathione. Trichloroethylene metabolism in mice, rats, and humans is qualitatively similar, producing the same primary metabolites, which include chloral hydrate, dichloroacetic acid, and trichloroacetic acid. These primary toxic metabolites, produced by the P450 pathway, are associated with liver and lung toxicity in rats and mice. Another metabolite produced by the glutathione pathway, dichlorovinylcysteine, is associated with kidney toxicity. Dichlorovinylcysteine can undergo bioactivation in the kidney to chemical species that can react with cellular proteins; however, the National Research Council reported that no studies were available on its carcinogenic potential (NRC 2006).

Kidney tumors (renal-cell carcinoma) from workers occupationally exposed to high levels of trichloroethylene exhibited somatic mutations of the von Hippel-Lindau tumor-suppressor gene (*VHL*), which has been associated with renal-cell carcinoma (Brauch *et al.* 1999). Mutations in *VHL* were found in 75% of renal-cell carcinomas from 44 trichloroethylene-exposed workers. DNA sequencing analysis showed that 39% of these tumors had a specific mutation, a C to T transition at nucleotide 454, resulting in a change from proline to serine at codon 81. In four patients, the nucleotide 454 mutation was also found in the nearby noncancerous kidney tissue. Moreover, this mutation was specific to trichloroethylene exposure, because it was not found in renal-cell tumors from patients not exposed to trichloroethylene, and it was related to the disease, because it was not found in germline DNA from either diseased or nondiseased individuals.

It is reasonable from a biological perspective that the kidney tumors observed in humans are related to trichloroethylene exposure

because (1) the site and histopathological characteristics of the tumors in humans and experimental animals are similar (Vamvakas *et al.* 1993, NRC 2006), (2) a portion of the molecular mechanism of this type of cancer (nephrocarcinogenicity) has been discovered (Dekant *et al.* 1986, IARC 1995, Bernauer *et al.* 1996), (3) the metabolites derived from trichloroethylene (the likely ultimate electrophilic intermediates of its bioactivation) are identical in humans and experimental animals (Birner *et al.* 1993, Clewell *et al.* 1995, IARC 1995), and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of trichloroethylene (Birner *et al.* 1993), humans appear to be more sensitive than rats in developing the primary biochemical lesion that precedes kidney cancer.

In general, trichloroethylene and most of its major metabolites (chloral hydrate, dichloroacetic acid, and trichloroacetic acid) are not potent genotoxicants in a broad range of bacterial, lower eukaryotic, and *in vitro* and *in vivo* mammalian test systems (NTP 2000). In mammalian cell-culture studies, trichloroethylene did not cause chromosomal aberrations in Chinese hamster ovary (CHO) cells, unscheduled DNA synthesis in rat hepatocytes, or gene mutations in human lymphoblastoid cells, but it did cause sister chromatid exchange in CHO cells, gene mutations in mouse lymphoma cells, and morphological transformation of rat embryo cells. In rodent *in vivo* studies, trichloroethylene did not induce unscheduled DNA synthesis, sister chromatid exchange, dominant lethal mutations, or chromosomal aberrations. Trichloroethylene gave mixed results for DNA single-strand breaks or alkali-labile sites in mouse liver and for micronucleus formation in mice. Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchange in peripheral lymphocytes of workers exposed to trichloroethylene were inconclusive. The trichloroethylene metabolite dichlorovinylcysteine was mutagenic in *Salmonella typhimurium* and may cause DNA damage in mammalian cells *in vitro* and *in vivo*.

Properties

Trichloroethylene is a halogenated alkene that exists at room temperature as a clear, colorless, or blue mobile liquid with an ethereal odor. It is slightly soluble in water, soluble in ethanol, acetone, diethyl ether, and chloroform, and miscible in oil. It is relatively stable, but oxidizes slowly when exposed to sunlight in air (IARC 1976). Upon combustion, trichloroethylene produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, it breaks down into hydrochloric acid (HSDB 2009). Physical and chemical properties of trichloroethylene are listed in the following table.

Property	Information
Molecular weight	131.4
Specific gravity	1.4642 at 20°C/4°C
Melting point	-84.7°C
Boiling point	87.2°C
Log K_{ow}	2.61
Water solubility	1.28 g/L at 25°C
Vapor pressure	69 mm Hg at 25°C
Vapor density relative to air	4.53

Source: HSDB 2009.

Use

Trichloroethylene is used mainly as an intermediate for hydrofluorocarbon production (67%) and as a degreaser for metal parts (30%) (CMR 2005). The remaining 3% is used primarily as a modifier for polyvinyl chloride polymerization. Five main industrial groups use trichloroethylene in vapor or cold degreasing operations: furniture and fixtures production, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous man-

ufacturing industries. Trichloroethylene is used as a solvent in the rubber industry, adhesive formulations, dyeing and finishing operations, printing inks, paints, lacquers, varnishes, adhesives, and paint strippers (IARC 1995). Trichloroethylene has also been used as an extraction solvent for natural fats and oils, as a solvent in extracting spices, hops, and decaffeinated coffee, and as an anesthetic and analgesic in obstetrics and for minor surgical procedures.

Production

Two U.S. companies had a combined annual trichloroethylene production capacities of 160,000 tons (320 million pounds) in 1992 (IARC 1995) and 330 million pounds in 2005 (CMR 2005). In 2009, trichloroethylene was produced by 22 manufacturers worldwide, including two in the United States (SRI 2009), and was available from 103 suppliers, including 39 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of trichloroethylene totaled between 100 million and 500 million pounds between 1986 and 2006 except in 1994, when the quantity was between 50 million and 100 million pounds (EPA 2004, 2009). U.S. imports of trichloroethylene have generally increased since 1989, with a low of 329,000 kg (705,000 lb) in 1992 and a high of 27.2 million kilograms (60 million pounds) in 2007. During this period, U.S. exports of trichloroethylene ranged from a low of 16.6 million kilograms (36.7 million pounds) in 2005 to a high of 48.7 million kilograms (107.4 million pounds) in 1992. Exports in 2007 were 25 million kilograms (55 million pounds).

Trichloroethylene is reported to occur naturally in some algae in temperate to tropical climates and in one red macroalga (IARC 1995).

Exposure

Inhalation is the main route of potential exposure to trichloroethylene. Trichloroethylene is a major ingredient in numerous consumer products. For example it is listed as a major ingredient of 12 household aerosol products, constituting 80% to 100% of three products and 90% to 99% of two other products used as cleaners or degreasers and intended for use primarily in hobbies, crafts, and home maintenance (HPD 2009). Trichloroethylene has also been present in typewriter correction fluids, paint removers and strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg 1995). Trichloroethylene is no longer used as an extraction solvent for cosmetics or drug products or as a drycleaning agent (IARC 1995).

Trichloroethylene was identified in 72 food items in the U.S. Food and Drug Administration's Total Diet Study, including fruits, beverages, and many foods prepared with oils and fats. The highest mean concentration was found in samples of raw avocado (FDA 2006). Other studies also have found trichloroethylene in a variety of foods, with the highest levels in meats and margarine. Trichloroethylene was at one time used extensively as a solvent for extraction of natural fats and oils, spices, hops, and caffeine (from coffee), but the FDA imposed limitations on these uses in 1977. The trichloroethylene found in foods is believed to come from the use of contaminated water in food processing or from food-processing equipment cleaned with trichloroethylene (ATSDR 1997).

According to EPA's Toxics Release Inventory, environmental releases of trichloroethylene have declined steadily since 1988, when over 57 million pounds was released. In 2008, 306 facilities released a total of 3.6 million pounds of trichloroethylene. Of these facilities, 256 reported point- or area-source releases to air ranging from 0.22 to nearly 264,000 lb, and 15 facilities released a total of 435 lb to water (TRI 2010). Mean background levels of trichloroethylene in air were reported to range from 0.03 ppb (0.16 $\mu\text{g}/\text{m}^3$) in rural areas to

0.46 ppb (2.5 $\mu\text{g}/\text{m}^3$) in urban and suburban areas. In areas near emission sources, trichloroethylene was measured in air at concentrations of up to 1.2 ppb (6.4 $\mu\text{g}/\text{m}^3$) (ATSDR 1997). From 1985 to 1998, EPA's Aerometric Information Retrieval System obtained 1,200 ambient-air measurements of trichloroethylene from various state and local environmental agencies in 25 states. In 1998, 115 monitors in 14 states detected trichloroethylene at a mean concentration of 0.88 $\mu\text{g}/\text{m}^3$ (range = 0.01 to 3.9 $\mu\text{g}/\text{m}^3$). Based on this average concentration and a daily inhalation rate of 20 m^3 of air, the daily inhalation exposure to trichloroethylene was estimated at 18 μg (Wu and Schaum 2000).

Trichloroethylene concentrations were measured during EPA's large-scale Total Exposure Assessment Methodology studies conducted in Maryland, New Jersey, and California from 1981 through 1987 (Wallace *et al.* 1996). Trichloroethylene exposure concentrations were measured with personal air monitors carried by 750 individuals for 24 hours. The median personal air concentrations were 0.3 to 3.0 $\mu\text{g}/\text{m}^3$. Expired-breath samples taken from the same subjects in the evenings after several hours at home (from 50 to 350 individuals in two New Jersey cities in 1981 to 1983 and 75 individuals in two California towns in 1984) contained trichloroethylene at concentrations of 0.1 to 0.9 $\mu\text{g}/\text{m}^3$ (the median personal air concentrations ranged from 1.7 to 3.0 $\mu\text{g}/\text{m}^3$). However, trichloroethylene was not detected in the breath of 140 individuals in Los Angeles, California, in 1984 or 1987 (with trichloroethylene personal air levels ranging from 0.3 to 1.2 $\mu\text{g}/\text{m}^3$) or in the breath of 75 individuals in Baltimore, Maryland, in 1987 (with trichloroethylene personal air levels averaging 1.1 $\mu\text{g}/\text{m}^3$). As part of the Minnesota Children's Pesticide Exposure Study, personal, indoor-air, and outdoor-air trichloroethylene concentrations were measured in 284 households with children. The median values for indoor, outdoor, and personal sampling all were between 0.5 and 1 $\mu\text{g}/\text{m}^3$ (Adgate *et al.* 2004).

Trichloroethylene is a common groundwater and drinking-water contaminant (Gist and Burg 1995, IARC 1995, ATSDR 1997, Wu and Schaum 2000). Industrial wastewater is a source of trichloroethylene released into surface-water systems. Trichloroethylene background levels in 1995 were 0.001 ppb ($\mu\text{g}/\text{L}$) in the Gulf of Mexico, 0.007 ppb in the northeastern Atlantic Ocean, and 0.0008 to 0.039 ppb in rainwater and snow (Gist and Burg 1995). In EPA's Contract Laboratory Program Statistical Database, trichloroethylene occurred in about 3% of surface-water samples and 19% of groundwater samples (IARC 1995). Trichloroethylene readily volatilizes from tap water, and exposure from inhalation of volatilized trichloroethylene from contaminated tap water may equal or exceed the exposure from ingestion of contaminated drinking water. One study estimated that inhalation exposure from a 10-minute shower in trichloroethylene-contaminated water would equal the exposure expected from drinking the contaminated water. Bathing in contaminated water would also contribute a significant fraction of an individual's total dermal exposure. Based on a trichloroethylene concentration of 3.0 $\mu\text{g}/\text{L}$ (the median concentration in a large California water survey) and daily water consumption of 2 L, average daily trichloroethylene exposure through ingestion of drinking water was estimated as 6 μg (Wu and Schaum 2000). This estimate is consistent with ATSDR's (1997) estimate of 2 to 20 μg for the general population.

In the Third National Health and Nutrition Examination Survey (conducted from 1988 to 1994), trichloroethylene concentrations were measured in whole-blood samples from 677 people of all ages, races, genders, and geographical regions who were not occupationally exposed to trichloroethylene. The results suggested that 10% of the U.S. population had detectable levels of trichloroethylene in their blood (detection limit = 0.01 $\mu\text{g}/\text{L}$) (Wu and Schaum 2000). Assuming that people in whose blood TCE was not detected had blood con-

centrations of half the detection limit, the mean concentration of trichloroethylene in blood was 0.017 µg/L.

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 401,373 workers at 23,225 facilities potentially were exposed to trichloroethylene (NIOSH 1990). During health hazard evaluations by the National Institute for Occupational Safety and Health, mean occupational exposure concentrations of trichloroethylene in air ranged from 1.3 mg/m³ to 1,084 mg/m³ (for short-term exposure); the highest mean concentration was for a degreasing operation (IARC 1995).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of trichloroethylene on ships and barges.

Department of Transportation (DOT)

Trichloroethylene is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.
New Source Performance Standards: Manufacture of trichloroethylene is subject to certain provisions for the control of volatile organic compound emissions.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 2.5 µg/L; based on fish or shellfish consumption only = 30 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.5 mg/L.
Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of trichloroethylene = U228, F001, F002, F024, F025, K018, K019, K020.
Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.005 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.005 mg/L.

Trichloroethylene may be used as a solvent in the manufacture of modified hop extract provided the residue does not exceed 150 ppm.

Trichloroethylene may be used as a solvent in the manufacture of specified foods with maximum residue levels ranging from 10 to 30 ppm.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 100 ppm.

Ceiling concentration = 200 ppm.

Acceptable peak exposure = 300 ppm (5 min in any 2 h).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

Threshold limit value – short-term exposure limit (TLV-STEL) = 25 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 25 ppm (10-h TWA).

Ceiling recommended exposure limit = 2 ppm (60-min ceiling) during use as an anesthetic agent.

Immediately dangerous to life and health (IDLH) limit = 1,000 ppm.

Listed as a potential occupational carcinogen.

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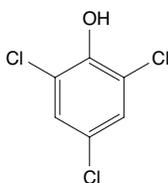
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2,4,6-Trichlorophenol

CAS No. 88-06-2

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)



Carcinogenicity

2,4,6-Trichlorophenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 2,4,6-trichlorophenol caused tumors in two rodent species and at several different tissue sites. Administered in the diet, 2,4,6-trichlorophenol caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in mice of both sexes and lymphoma or mononuclear-cell leukemia in male rats (NCI 1979, IARC 1982).

Cancer Studies in Humans

No studies were identified that evaluated the relationship between human cancer and exposure specifically to 2,4,6-trichlorophenol.

Properties

2,4,6-Trichlorophenol is a chlorinated phenolic compound that exists at room temperature as colorless to yellow crystals with a strong phenolic odor (IARC 1979, 1999, HSDB 2009). It is practically insoluble in water but soluble in ethanol, diethyl ether, hot acetic acid, benzene, carbon tetrachloride, methanol, Stoddard solvent, toluene, and turpentine. It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 2,4,6-trichlorophenol are listed in the following table.

Property	Information
Molecular weight	197.5
Specific gravity	1.4901
Melting point	69°C
Boiling point	246°C
Log K_{ow}	3.69
Water solubility	0.800 g/L at 25°C
Vapor pressure	0.008 mm Hg at 25°C
Dissociation constant (pK_a)	6.23 at 25°C

Source: HSDB 2009.

Use

2,4,6-Trichlorophenol has been used primarily in various pesticide formulations and as a wood preservative. It has been used as a fungicide, glue preservative, insecticide, bactericide, defoliant, herbicide, and anti-mildew agent for textiles (IARC 1979, HSDB 2009). Most uses of 2,4,6-trichlorophenol were canceled in the United States; however, it continues to be used in the synthesis of some fungicides (HSDB 2009). Trichlorophenol has been reported to be used in a mixture as a disinfectant and antiseptic in the treatment of Guinea worm ulcers in Africa, but the information reported did not indicate whether the product contained the 2,4,6-trichlorophenol isomer (Ogunniyi *et al.* 2000).

Production

Commercial production of 2,4,6-trichlorophenol in the United States was first reported in 1950 (IARC 1979). In 1975, production was discontinued by the only U.S. manufacturer because of the high cost of removing chlorinated dibenzo-*p*-dioxins, which occurred as toxic impurities (HSDB 2009). In 2009, 2,4,6-trichlorophenol was produced by one manufacturer each in China, India, and Europe (SRI 2009) and was available from 27 suppliers worldwide, including 16 U.S. suppliers (ChemSources 2009). U.S. imports of 2,4,6-trichlorophenol totaled 2,200 lb in 1976, 600 lb in 1978, and 550 lb in 1980 (IARC 1979, HSDB 2009).

Exposure

The routes of potential human exposure to 2,4,6-trichlorophenol are inhalation, ingestion, and dermal contact. The general population may be exposed to 2,4,6-trichlorophenol through ingestion of contaminated food or water or inhalation of contaminated air (IARC 1979, HSDB 2009). According to the National Cancer Institute (NCI 1979), substantial exposure of the general population was questionable; however, residues may be present throughout the environment, because 2,4,6-trichlorophenol was widely used as a pesticide. 2,4,6-Trichlorophenol can also form when industrial wastewater containing phenol or certain aromatic acids is treated with hypochlorite or during the disinfection of drinking-water sources. Trichlorophenol (unspecified isomers) has been detected in ambient air and in samples of river water, landfill leachate, chemical plant effluent water, sewage treatment plant effluent, and tap water (ATSDR 1999, HSDB 2009).

2,4,6-Trichlorophenol is a precursor of 2,4,6-trichloroanisole, which is believed to be a potential cause of "cork taint" in wine (Soleas *et al.* 2002). In one study, 80% of spoiled wines contained 2,4,6-trichloroanisole (Insa *et al.* 2006). 2,4,6-Trichlorophenol was measured in cork samples at mean concentrations of up to 26 ng/g (0.026 µg/g) and in oak barrels used for aging wine at up to 0.8 µg/g (Pizarro *et al.* 2006). The efficiency with which trichlorophenol is converted to trichloroanisole depends on the microorganisms present in the cork. Trichlorophenol may also cause off odors in potato chips, dried fruit, coffee, and drinking water (Alvarez-Rodriguez *et al.* 2002). It was measured in coffee at concentrations of up to 42 ppb (0.042 µg/g) (Spadone *et al.* 1990) and in semi-bleached-paper dishes and napkins at 0.075 µg/g (Ozaki *et al.* 2004).

According to the U.S. Environmental Protection Agency's Toxics Release Inventory, environmental releases of 2,4,6-trichlorophenol totaled 12,310 lb in 1988. Releases declined by nearly 99% from 1988 to 1990 and remained at about the same level from 1990 to 1999, but in 2005 returned to nearly the same level as in 1988. In 1988 and 2005, over 88% was released to underground injection wells. In 2007, four facilities released a total of 513 lb (TRI 2009). In air, 2,4,6-trichlorophenol is degraded by reaction with photochemically produced hydroxyl radicals, with a half-life of 26 days. In surface water, 2,4,6-tri-

chlorophenol is expected to dissociate somewhat. It may adsorb to sediment and suspended particles or volatilize from water, with a half-life of 20 days in a river and 150 days in a lake model. It has a high potential for bioconcentration in aquatic organisms. When released to moist soil, 2,4,6-trichlorophenol is expected to somewhat dissociate. The portion that does not dissociate is expected to remain relatively immobile; however, 2,4,6-trichlorophenol is subject to some biodegradation in soil, with a half-life of 5 to 20 days (HSDB 2009).

In the United States, 2,4,6-trichlorophenol was measured in the atmosphere at a median concentration of 0.3 µg/m³. It was detected in groundwater at concentrations of up to 91.3 ppb, in surface water in Canada at up to 30 ppb, in sediments of Canadian streams at up to 10 mg/kg (10,000 ppb), and in snow in Finland at 0.509 ppb (HSDB 2009). 2,4,6-Trichlorophenol was measured in runoff downgradient from 43 Finnish waste sites at a median concentration of 0.11 µg/L (Assmuth 1996). It was found in finished drinking water in the United States, Finland, and Canada at concentrations of 14 to 700 ppt (0.014 to 0.7 ppb) and in goldfish in New Zealand at up to 40.5 ppb (HSDB 2009).

Average daily intake of 2,4,6-trichlorophenol in Finland was estimated to be 50 µg (HSDB 2009). In urine samples collected from 1,000 adults in the U.S. general population as a part of the Third National Health and Nutrition Examination Survey (conducted from 1988 to 1994), 2,4,6-trichlorophenol was detected in 9.5% of the samples, and the 90th-percentile concentration was 3.3 µg/L (Hill *et al.* 1995). The Centers for Disease Control and Prevention reported that 2,4,6-trichlorophenol was present in urine from 5 of 30 volunteers with no known occupational exposures to phenols, at a median concentration of 0.3 ng/mL (0.3 µg/L) (Ye *et al.* 2005) and in 5% of 20 samples of breast milk from women with no known exposure to 2,4,6-trichlorophenol (Ye *et al.* 2006). 2,4,6-Trichlorophenol was detected in the urine of 37% of the general population of Germany, at a mean concentration of 0.6 µg/g of creatinine (IARC 1979).

The potential for occupational exposure to 2,4,6-trichlorophenol is greatest for workers involved in wood preservation or the production of chlorophenols or chemicals made from chlorophenols and for workers in hospitals and in the leather tanning and finishing industry (ATSDR 1999, HSDB 2009). 2,4,6-Trichlorophenol was found in the urine of workers at a hazardous-waste incinerator in 1999–2000 at mean concentrations of up to 3.5 µg/g of creatinine (Schuhmacher *et al.* 2002); in more than half of the urine samples from harbor workers exposed to river silt aerosols in Hamburg, Germany, at mean concentrations of up to 0.39 µg/g of creatinine (Radon *et al.* 2004); and in the urine of sawmill workers at up to 2,000 µg/L. High urinary levels of trichlorophenol were also reported for lindane production workers and municipal waste incinerator workers (0.85 µg/g of creatinine) (IARC 1979, HSDB 2009). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 851 workers (chemists), including 187 women, potentially were exposed to 2,4,6-trichlorophenol (NIOSH 1990).

Regulations

Department of Transportation (DOT)

2,4,6-Trichlorophenol is considered a hazardous material, and special requirements have been set for transporting this material in tank cars.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Clean Water Act

Designated a hazardous substance.

Effluent Guidelines: Chlorinated phenols are listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 1.4 µg/L; based on fish or shellfish consumption only = 2.4 µg/L; based on organoleptic-effect criteria = 2.0 µg/L.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 2.0 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of 2,4,6-trichlorophenol = F027, K043, K099, K105.

Listed as a hazardous constituent of waste.

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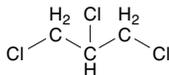
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1,2,3-Trichloropropane

CAS No. 96-18-4

Reasonably anticipated to be a human carcinogen

First listed in the *Eighth Report on Carcinogens* (1998)



Carcinogenicity

1,2,3-Trichloropropane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Oral exposure to 1,2,3-trichloropropane caused tumors at several different tissue sites in mice and rats. Administration of 1,2,3-trichloropropane by stomach tube increased the combined incidence of benign and malignant tumors of the forestomach (squamous-cell papilloma and carcinoma) in mice and rats of both sexes. In mice of both sexes, it also increased the combined incidence of benign and malignant liver tumors (hepatocellular carcinoma and adenoma) and caused benign Harderian-gland tumors (adenoma). In rats of both sexes and in female mice, it caused benign and/or malignant tumors of the oral mucosa (squamous-cell papilloma and/or carcinoma). In rats, oral exposure to 1,2,3-trichloropropane also caused cancer of the Zymbal gland (carcinoma) in both sexes, cancer of the mammary gland (carcinoma) in females, and benign tumors (adenoma) of the kidney and pancreas in males, and it increased the combined incidence of benign and malignant tumors (adenoma and carcinoma) of the preputial gland in males and the clitoral gland in females. In female mice, it also caused benign and malignant tumors of the uterus (adenoma, stromal polyp, and adenocarcinoma) (NTP 1993, IARC 1995, Irwin *et al.* 1995).

Since 1,2,3-trichloropropane was listed in the *Eighth Report on Carcinogens*, an additional study in experimental animals has been identified. Exposure to 1,2,3-trichloropropane in the aquarium water of guppies (*Poecilia reticulata*) and medaka (*Oryzias latipes*) caused liver tumors in males and females of both species and benign gallbladder tumors (papillary adenoma) in medaka of both sexes (NTP 2005).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 1,2,3-trichloropropane.

Studies on Mechanisms of Carcinogenesis

1,2,3-Trichloropropane caused gene mutations in bacteria, yeast, and mammalian cells and sister chromatid exchange, chromosomal aberrations, micronucleus formation, and morphological transformation in mammalian cells *in vitro* (IARC 1995, Doherty *et al.* 1996). 1,2,3-Trichloropropane was active almost exclusively in the presence of mammalian microsomal metabolic activation or when tested in metabolically competent cells. In rats and mice exposed by gavage or intraperitoneal injection, 1,2,3-trichloropropane caused DNA damage, including formation of DNA adducts, in several different tissues (IARC 1995, La *et al.* 1995). 1,2,3-Trichloropropane also caused cell proliferation at several tissue sites in rats and mice exposed by gavage

and rats exposed by inhalation (Johannsen *et al.* 1988, NTP 1993, Irwin *et al.* 1995). 1,2,3-Trichloropropane was reported not to cause dominant lethal mutations in male rats (IARC 1995).

Several metabolites of 1,2,3-trichloropropane, including 1,3-dichloroacetone, caused genetic damage in various short-term test systems (IARC 1995). 1,3-Dichloroacetone is produced by human liver microsomes, although at a lower rate of formation than in rats (Weber and Sipes 1992). Two 1,2,3-trichloropropane analogues, 1,2-dibromo-3-chloropropane and 1,2-dibromoethane (ethylene dibromide), are listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*.

Properties

1,2,3-Trichloropropane is a halogenated alkane that exists at room temperature as a colorless to straw-colored liquid with an odor similar to that of trichloroethylene or chloroform (IPCS 2003). It is slightly soluble in water and soluble in chloroform, ethanol, and diethyl ether (IARC 1995). It is stable under normal temperatures and pressures (Akron 2009). Physical and chemical properties of 1,2,3-trichloropropane are listed in the following table.

Property	Information
Molecular weight	147.4
Specific gravity	1.3889 at 20°C/4°C
Melting point	-14.7°C
Boiling point	156.85°C
Log K_{ow}	2.27
Water solubility	1.8 g/L at 25°C
Vapor pressure	3.69 at 25°C
Vapor density relative to air	5.1

Source: HSDB 2009.

Use

1,2,3-Trichloropropane is used primarily as a chemical intermediate in the production of polysulfone liquid polymers, dichloropropene, and hexafluoropropylene, and as a cross-linking agent in the synthesis of polysulfides (ATSDR 1992). No data were found to indicate the extent to which 1,2,3-trichloropropane is currently used for these purposes. In the past, 1,2,3-trichloropropane was used primarily as a solvent and extracting agent (ATSDR 1992, IARC 1995). As a solvent, it was commonly used as a cleaning and maintenance solvent, paint and varnish remover, and degreasing agent. No indication was found that it continues to be used for these purposes (ATSDR 1992). 1,2,3-Trichloropropane was formulated with dichloropropenes in the manufacture of the soil fumigant D-D (IARC 1995), which is no longer available in the United States (Sine 1991).

Production

Estimates for the production of 1,2,3-trichloropropane in the United States in 1977 ranged from 21 million to 110 million pounds (ATSDR 1992). In 2009, 1,2,3-trichloropropane was produced by five manufacturers worldwide, including two in the United States (SRI 2009), and was available from 22 suppliers, including 15 U.S. suppliers (Chem-Sources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule indicated that U.S. production plus imports of 1,2,3-trichloropropane totaled 10 million to 50 million pounds in 1986, 1990, and 1998 and 1 million to 10 million pounds in 2002 (EPA 2004). No data were found on U.S. imports or exports of 1,2,3-trichloropropane.

1,2,3-Trichloropropane may also be produced in significant quantities as a by-product of the production of other compounds, such as epichlorohydrin, dichloropropene, propylene oxide, propylene chlorohydrin, dichlorohydrin, and glycerol (ATSDR 1992, IPCS 2003).

Exposure

The general population may potentially be exposed to low levels of 1,2,3-trichloropropane through ingestion of contaminated well water or inhalation of contaminated air. Exposure is more likely for individuals who live near facilities that use or produce 1,2,3-trichloropropane or near hazardous waste disposal facilities (ATSDR 1992). In the U.S. Food and Drug Administration's Total Diet Study, 1,2,3-trichloropropane was detected in one sample of boiled fresh or frozen green beans at a concentration of 0.018 ppm (18 µg/kg) (FDA 2006). In the past, inhalation and dermal exposure likely occurred during the use of consumer products that contained 1,2,3-trichloropropane, such as certain paint and varnish removers and cleaning agents; however, it has been reported that 1,2,3-trichloropropane is no longer used in consumer products (ATSDR 1992).

Releases to the environment are likely to occur as a result of manufacture, formulation, and use of products containing 1,2,3-trichloropropane as a contaminant, such as soil fumigants and well-drilling aids (HSDB 2009, IPCS 2003). According to EPA's Toxics Release Inventory, environmental releases of 1,2,3-trichloropropane from 1995 to 2003 ranged from a low of 2,091 lb in 1996 to a high of 98,000 lb in 2002 (TRI 2009). The largest releases have been to air. In 2003, seven facilities reported releases of 14,256 lb, of which 65% was released to air and 26% to surface water; 98% of waste containing 1,2,3-trichloropropane was managed on site. If released to air, 1,2,3-trichloropropane is expected to exist as a vapor, because of its high vapor pressure (HSDB 2009). In air, it may react with photochemically produced hydroxyl radicals, with an estimated half-life of 46 days. If released to water, it will most likely volatilize, with an estimated half-life of 6.7 hours in river models and 5.7 days in lake models. If released to land, it is expected either to volatilize from surface soil or to leach into groundwater.

No measurements of 1,2,3-trichloropropane in air in the United States were found. In 1976, 1,2,3-trichloropropane was detected qualitatively in 1 of 30 surface-water samples from the Delaware, Schuylkill, and Lehigh rivers (ATSDR 1992). It was found in nearly half of municipal sewage sludge samples collected in Michigan in 1980, at a median concentration of 0.35 mg/kg on a dry-weight basis, and in U.S. groundwater wells at concentrations of up to 10 µg/L (ATSDR 1992, Tesoriero *et al.* 2001). In Osaka, Japan, it was found in 18 samples of surface water from urban rivers and their estuaries, at concentrations ranging from the detection limit (0.18 µg/L) to 100 µg/L (Yamamoto *et al.* 1997). 1,2,3-Trichloropropane has been identified as a contaminant at eight hazardous-waste sites on EPA's National Priorities List (ATSDR 1992).

1,2,3-Trichloropropane is manufactured in closed systems; therefore, occupational exposures are more likely to occur at facilities where it is used than at facilities where it is produced (ATSDR 1992). Direct handling of 1,2,3-trichloropropane or products containing 1,2,3-trichloropropane may occur during purification, formulation of products, sampling, quality control, packaging and storage, leakage of equipment, startup and shutdown procedures, maintenance, cleanup, and spills or other facility emergencies. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 492 workers (in the Chemicals and Allied Products industry), including 10 women, potentially were exposed to 1,2,3-trichloropropane (NIOSH 1990).

Regulations

Coast Guard, Department of Homeland Security

Minimum requirements have been established for safe transport of 1,2,3-trichloropropane on ships and barges.

Environmental Protection Agency (EPA)

Clean Air Act

New Source Performance Standards: Manufacture or use is subject to certain provisions for the control of volatile organic compound emissions.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed as a hazardous constituent of waste.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 50 ppm (300 mg/m³).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 10 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 10 ppm (60 mg/m³).

Immediately dangerous to life and health (IDLH) limit = 100 ppm.

Listed as a potential occupational carcinogen.

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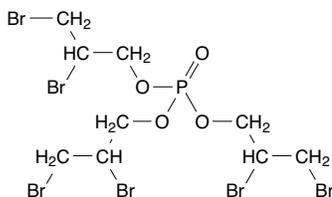
Tris(2,3-dibromopropyl) Phosphate

CAS No. 126-72-7

Reasonably anticipated to be a human carcinogen

First listed in the *Second Annual Report on Carcinogens* (1981)

Also known as TRIS



Carcinogenicity

Tris(2,3-dibromopropyl) phosphate is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Tris(2,3-dibromopropyl) phosphate caused tumors in two rodent species, at several different tissue sites, and by two different routes of administration. Dietary administration of tris(2,3-dibromopropyl) phosphate caused benign or malignant tumors of the forestomach (squamous-cell papilloma or carcinoma) and lung (bronchiolar/alveolar adenoma or carcinoma) in mice of both sexes; the kidney (tubular-cell adenoma or adenocarcinoma) in male mice and in rats of both sexes; and the liver (hepatocellular adenoma or carcinoma) in female mice (NCI 1978). Dermal exposure to tris(2,3-dibromopropyl) phosphate caused tumors of the skin, forestomach, lung, and oral cavity in female mice (IARC 1979).

Since tris(2,3-dibromopropyl) phosphate was listed in the *Second Annual Report on Carcinogens*, an additional study in rodents has been identified. In a study of limited duration, administration of tris(2,3-dibromopropyl) phosphate by stomach tube caused benign colon tumors in male rats (IARC 1987, 1999).

Cancer Studies in Humans

The data available from epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to tris(2,3-dibromopropyl) phosphate.

Properties

Tris(2,3-dibromopropyl) phosphate is a haloalkyl phosphate that is a pale-yellow viscous liquid at room temperature. It is practically insoluble in water but is miscible with carbon tetrachloride, chloroform, and methylene chloride. It is stable in sunlight or at temperatures up to 200°C but is hydrolyzed by acids and bases (Akron 2009, IARC 1979). Physical and chemical properties of tris(2,3-dibromopropyl) phosphate are listed in the following table.

Property	Information
Molecular weight	697.6 ^a
Specific gravity	2.27 at 25°C ^a
Freezing point	5.5°C ^a
Boiling point	390°C ^b
Log K_{ow}	4.29 ^a
Water solubility	8 mg/L at 24°C ^a
Vapor pressure	2.25×10^{-4} mm Hg at 25°C ^a

Sources: ^aHSDB 2009, ^bIARC 1999.

Use

Tris(2,3-dibromopropyl) phosphate was used in the United States for making flame-retardant children's clothing (IPCS 1995). In 1977, the Consumer Product Safety Commission banned the use of tris(2,3-dibromopropyl) phosphate in children's clothing and in fabric, yarn, and fiber when intended for use in such clothing (CPSC 1977). Tris(2,3-dibromopropyl) phosphate has also been used as a flame retardant in polyurethane foams for cushioning, insulation, furniture, and automobile and aircraft interior parts, as well as in polystyrene foam, acrylic carpets and sheets, water flotation devices, polyvinyl and phenolic resins, paints, lacquers, paper coatings, styrene-butadiene rubber, and latexes (IARC 1979, 1999).

Production

Tris(2,3-dibromopropyl) phosphate was first produced in 1950 (IPCS 1995), and commercial production in the United States was first reported in 1959 (IARC 1979, 1999). In 1975, U.S. production was estimated at between 4.1 million and 5.4 million kilograms (9 million and 12 million pounds) (IARC 1979, IPCS 1995, HSDB 2009). In 2009, no commercial manufacturers of tris(2,3-dibromopropyl) phosphate were identified, but it was available from six U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of tris(2,3-dibromopropyl) phosphate were found.

Exposure

The routes of potential human exposure to tris(2,3-dibromopropyl) phosphate are inhalation, dermal contact, and ingestion (NCI 1978). Because tris(2,3-dibromopropyl) phosphate is no longer reported to be produced in the United States, the potential for exposure should be small. The chemical was widely used in children's sleepwear and mattresses in the past. Exposure and environmental release could have occurred during the manufacture of flame-retardant material or leaching during use or washing. The treated garments could contain 5% to 10% tris(2,3-dibromopropyl) phosphate by weight (NCI 1978, IPCS 1995). The tris(2,3-dibromopropyl) phosphate metabolite 2,3-dibromo-1-propanol was found at concentrations of up to 29 ng/mL in the urine of children wearing treated polyester pajamas, and dermal absorption of tris(2,3-dibromopropyl) phosphate was estimated at 9 µg/kg of body weight per day (IARC 1979).

Tris(2,3-dibromopropyl) phosphate does not occur naturally, but it has been detected in food and water. The U.S. Environmental Protection Agency estimated in 1976 that as much as 10% of U.S. tris(2,3-dibromopropyl) phosphate production entered the environment from textile finishing plants and laundries and that the remainder was disposed of as solid waste (IARC 1979). EPA's Toxics Release Inventory reported environmental releases of tris(2,3-dibromopropyl) phosphate increasing from none in 1998 to 10 lb in 2000 and 260 lb in 2001. In 2002 and 2003, slightly over 300 lb of tris(2,3-dibromopropyl) phosphate was released by one facility, including 250 lb to surface water and nearly 60 lb to air. In 2005, 2006, and 2007, 250 lb was released to air and 10 lb to an off-site hazardous-waste landfill (TRI 2009).

When released to air, tris(2,3-dibromopropyl) phosphate is expected to exist in the vapor phase and to react with photochemically produced hydroxyl radicals, with a half-life of about 14 hours at 25°C. When released to surface water, it is expected to volatilize, with a half-life of 4 days in a model river and 38 days in a lake. Under basic conditions, it may hydrolyze in surface water; however, this is not expected to be a significant environmental fate process. It is not expected to bioaccumulate in aquatic organisms. When released to soil, tris(2,3-dibromopropyl) phosphate is expected to bind strongly to soil and sediment and to leach very slowly into groundwater. Tris(2,3-dibromopropyl) phosphate was detected at concentrations ranging from 44 to 85 ng/m³ in five air samples collected in 1976 and 1977 at two industrial facilities synthesizing organobromine compounds. In 1979, it was detected, but not quantified, in air and soil in the state of Arkansas (HSDB 2009).

The National Occupational Hazard Survey (conducted from 1972 to 1974) estimated that 29,000 workers, primarily in the Telephone Communication industry, potentially were exposed to tris(2,3-dibromopropyl) phosphate, (NIOSH 1976).

Regulations

Department of Transportation (DOT)

Tris(2,3-dibromopropyl) phosphate is considered a hazardous substance, and special requirements have been set for transporting it in tank cars.

Environmental Protection Agency (EPA)

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 10 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of tris(2,3-dibromopropyl) phosphate = U235.

Listed as a hazardous constituent of waste.

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Ultraviolet-Radiation-Related Exposures

Introduction

Ultraviolet radiation (UVR) is electromagnetic radiation found between X-radiation and light in the electromagnetic spectrum. It is emitted by the sun and artificial devices, including sunbeds or sunlamps. UVR can be divided into ultraviolet A (UVA), ultraviolet B (UVB), and ultraviolet C (UVC) radiation components.

Solar radiation and exposure to sunlamps or sunbeds were first listed in the *Ninth Report on Carcinogens* in 2000, and broad-spectrum UVR and its components (UVA, UVB, and UVC) were first listed in the *Tenth Report on Carcinogens* in 2002. Exposure to solar radiation and to sunlamps or sunbeds involves exposure to broad-spectrum UVR; therefore, these listings were combined for the *Tenth Report on Carcinogens*. The listings for exposures related to UVR are as follows:

- Solar radiation is *known to be a human carcinogen*.
- Exposure to sunlamps or sunbeds is *known to be a human carcinogen*.
- Broad-spectrum UVR is *known to be a human carcinogen*.
- Ultraviolet A radiation is *reasonably anticipated to be a human carcinogen*.
- Ultraviolet B radiation is *reasonably anticipated to be a human carcinogen*.
- Ultraviolet C radiation is *reasonably anticipated to be a human carcinogen*.

Much of the evidence for listing of the various UVR-related exposures applies to more than one type of UVR. For example, evidence for the carcinogenicity of broad-spectrum UVR comes from studies on solar radiation and on exposure to sunlamps or sunbeds. Similarly, studies that evaluated the carcinogenicity of solar radiation in experimental animals or the mechanism(s) by which sunlight causes cancer (mechanistic studies) involved exposure to broad-spectrum UVR or its UVA, UVB, or UVC components. Most of the information on mechanisms of carcinogenesis and on properties, use, production, exposure, and regulations is common to all listings for exposures related to UVR. Therefore, the carcinogenicity section for each of these listings is presented separately, and the other sections are combined.

Solar Radiation

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Solar radiation is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, which indicate that exposure to solar radiation causes skin cancer (malignant melanoma and non-melanocytic cancer). Some studies suggest that solar radiation may also be associated with melanoma of the eye and non-Hodgkin's lymphoma (IARC 1992).

Exposure to Sunlamps or Sunbeds

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Ninth Report on Carcinogens* (2000)

Carcinogenicity

Exposure to sunlamps or sunbeds is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. Sunlamps and sunbeds emit primarily UVA and UVB radiation. Epidemiological studies have shown that exposure to sunlamps or sunbeds increases the risk of malignant melanoma (Swerdlow *et al.* 1988, Walter *et al.* 1990, 1999, Autier *et al.* 1994, Westerdahl *et al.* 1994, 2000, Chen *et al.* 1998). The longer the exposure, the greater the risk, especially in individuals exposed before the age of 30 and individuals who have been sunburned. Malignant melanoma of the eye also is associated with exposure to sunlamps (IARC 1992).

Broad-Spectrum UVR

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Broad-spectrum UVR is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. Evidence that the broad-spectrum UVR component of solar radiation is carcinogenic comes from (1) studies of human cancer associated with exposure to devices that emit artificial broad-spectrum UVR, (2) the fact that tumors develop at the same tissue sites in humans exposed to sunlight and in animals exposed to broad-spectrum UVR from artificial sources, and (3) mechanistic studies in which human tissue was exposed to artificial sources of broad-spectrum UVR (see Studies on Mechanisms of Carcinogenesis, below).

Cancer Studies in Humans

Epidemiological studies have shown that exposure to broad-spectrum UVR from solar radiation causes skin cancer (malignant melanoma and non-melanocytic cancer) (IARC 1992). Studies of humans exposed to solar radiation, artificial devices emitting broad-spectrum UVR, or devices emitting predominantly UVA or UVB all contribute to these conclusions.

Cancer Studies in Experimental Animals

Exposure of albino rats and mice to broad-spectrum UVR caused benign and malignant skin tumors (papilloma, squamous-cell carcinoma, and spindle-cell sarcoma). Exposure to broad-spectrum UVR also caused malignant eye tumors in albino rats (spindle-cell sarcoma) and in hamsters (fibrosarcoma) (IARC 1992).

UVA

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVA is *reasonably anticipated to be a human carcinogen* based on (1) limited evidence of carcinogenicity from studies in humans and (2) sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Humans

Epidemiological studies on the effects of sunlight or artificial broad-spectrum UVR cannot identify effects due specifically to UVA, UVB,

or UVC exposure. However, information about the specific effects of UVA, UVB, and UVC exposure can be inferred by comparing the results of human epidemiology studies on the effects of specific UVR components in experimental animals and human tissues. In studies where most of the UVR exposure was to UVA (i.e., exposure to solar radiation or UVA-emitting sunbeds), exposure increased the risk of skin cancer. Exposure to sunbeds emitting mainly UVA (with 0.1% to 2.1% UVB) increased the risk of melanoma (Westerdahl *et al.* 2000).

Cancer Studies in Experimental Animals

Exposure to UVA caused benign and malignant skin tumors (papilloma and squamous-cell carcinoma) in mice (IARC 1992) and melanoma in fish (Setlow *et al.* 1993).

UVB

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVB is *reasonably anticipated to be a human carcinogen* based on (1) limited evidence of carcinogenicity from studies in humans and (2) sufficient evidence of carcinogenicity from studies in experimental animals. In addition, mechanistic studies with human tissue have demonstrated that the UVB component in solar radiation causes DNA damage (see Studies on Mechanisms of Carcinogenesis, below).

Cancer Studies in Humans

Epidemiological studies linking UVR exposure to skin cancer are limited because they lack information on the specific wavelengths of UVR to which the individuals were exposed. Increased risk of skin cancer is clearly associated with exposure to UVB (as a component of solar radiation or from sunlamps used before the early 1970s). However, the individuals in these studies were also exposed to other components of broad-spectrum UVR; therefore, the studies could not distinguish between the effects of UVB and other components of UVR. Sunlamps used in the early 1970s produced significant amounts of UVB (22% to 40%); one study found that exposure to UVB-emitting sunlamps increased the risk of malignant melanoma of the skin (Chen *et al.* 1998).

Cancer Studies in Experimental Animals

Prolonged exposure to devices emitting primarily UVB caused benign and/or malignant skin tumors in rats (papilloma), mice (papilloma, squamous-cell carcinoma, fibrosarcoma, and keratoacanthoma), guinea pigs (fibroma and trichofolliculoma), and opossums (melanocytic hyperplasia and melanoma) (IARC 1992).

UVC

CAS No.: none assigned

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

UVC is *reasonably anticipated to be a human carcinogen* based on (1) limited evidence of carcinogenicity from studies on mechanisms of carcinogenesis in human tissue and (2) sufficient evidence of carcinogenicity from studies in experimental animals. Mechanistic studies with human tissue have demonstrated that the UVC component

in solar radiation causes DNA damage (see Studies on Mechanisms of Carcinogenesis, below).

Cancer Studies in Experimental Animals

Exposure to high doses of radiation from devices emitting primarily UVC caused skin cancer in rats (keratoacanthoma-like tumors) and mice (squamous-cell carcinoma and fibrosarcoma) (IARC 1992).

Cancer Studies in Humans

No epidemiological studies have adequately evaluated the carcinogenicity of UVC in humans. UVC is absorbed by the ozone layer and does not contribute to UVR exposure from solar radiation. In studies of exposure to artificial devices emitting UVC, the devices also emitted other components of UVR.

Ultraviolet-Radiation-Related Exposures

Studies on Mechanisms of Carcinogenesis

Broad-spectrum UVR causes skin cancer via DNA damage, suppression of the immune system, tumor promotion, and mutations in the *p53* tumor-suppressor gene. Broad-spectrum UVR causes mutations in cultured human cells; the type of damage depends on the specific wavelength of UVR and whether the affected cells can repair the damage without error. DNA absorbs broad-spectrum UVR (mainly UVB and UVC), and this reaction yields products that can cause mutations (discussed below, under Properties). UVB causes the following four major DNA base modifications in humans: cyclobutane-type pyrimidine dimers, (6-4) photoproducts, the corresponding Dewar isomers, and thymine glycols. Both UVA and UVB induce 8-hydroxydeoxyguanosine production from guanosine by the action of singlet oxygen (Griffiths *et al.* 1998).

UVA, UVB, and UVC as individual components of broad-spectrum UVR have been shown to cause genetic damage in several *in vitro* test systems, including bacteria, yeast, rodent cells, and human cells. Moreover, exposure to each of the three components of broad-spectrum UVR causes DNA damage in humans. UVA's biological effects are indirect and largely the result of energy transferred through reactive oxygen intermediates, whereas UVB and UVC are absorbed by DNA and directly damage DNA through base modifications. Based on the numbers of studies showing genetic damage, UVC is the strongest genotoxin of the three components of broad-spectrum UVR, and UVA is the weakest.

More than 90% of human squamous-cell carcinomas contain mutations of the *p53* tumor suppressor gene. These mutations were found in 74% of sun-exposed normal human skin samples and only 5% of unexposed skin samples, indicating a strong association with sun exposure. Observed *p53* gene mutations were most frequently C to T or C:C to T:T transitions at pyrimidine-pyrimidine sequences. These specific *p53* mutations now are considered a signature of broad-spectrum UVR carcinogenesis (Brash *et al.* 1991, Ziegler *et al.* 1993, Griffiths *et al.* 1998, Wikonkal and Brash 1999).

Exposure to solar radiation and broad-spectrum UVR alters immune function in humans and experimental animals (IARC 1992). Evidence that immunosuppression is related to skin cancer comes from the following observations: (1) immunosuppressed organ transplant recipients showed a marked increase in skin cancer, particularly squamous-cell carcinoma, (2) broad-spectrum UVR decreased the ability to mount a delayed-type hypersensitivity response, and (3) mice exposed to low levels of broad-spectrum UVR failed to reject highly immunogenic tumor cell lines (Quinn 1997).

Exposure of human skin grafts on mice to UVB radiation caused precancerous lesions (melanocytic hyperplasia), and exposure to UVB after pretreatment with the carcinogen dimethylbenz[*a*]anthracene caused the grafts to develop human skin tumors (squamous-cell carcinoma, actinic keratoses, melanocytic hyperplasia, and melanoma) (Atilasoy *et al.* 1997).

Properties

Solar radiation includes most of the electromagnetic spectrum. Of the bands within the optical radiation spectrum, UVR is the strongest and most damaging to living things (IARC 1992). Broad-spectrum UVR includes wavelengths of light ranging from 100 to 400 nm. UVR is divided into wavelength ranges identified as UVA (315 to 400 nm), UVB (280 to 315 nm), and UVC (100 to 280 nm). Of the solar UV energy reaching the equator, 95% is UVA and 5% is UVB. No measurable UVC from solar radiation reaches the earth's surface, because the shortest UV wavelengths are completely absorbed by ozone, molecular oxygen, and water vapor in the upper atmosphere (Farmer and Naylor 1996).

Molecules that absorb UVR and visible light (photoreactive molecules) contain segments that react with light (called chromophores), in which photons of light excite electrons from the ground state to higher-energy states. These molecules then generally re-emit light on returning to lower-energy or ground states (Dyer 1965). The various molecules sensitive to UVR differ in the wavelengths of UVR that they absorb and the light that they emit. Photochemical and photobiological interactions occur when photons react with a photoreactive molecule, forming either an altered molecule or two separate molecules (Phillips 1983, Smith 1989). For such a reaction to occur, the photons must have enough energy to alter a photoreactive chemical bond (i.e., to break the original bond or form new bonds).

The photobiological reactions related to skin cancer risk due to UVR exposure are the reactions with the main chromophores of the skin's outer layer — urocanic acid, DNA, tryptophan, tyrosine, and the melanins. The products resulting from the reaction of UVR with DNA (DNA photoproducts) include pyrimidine dimers, pyrimidine-pyrimidone (6-4) photoproducts, thymine glycols, and DNA exhibiting cytosine and purine damage and other damage, such as DNA strand breaks and cross-links and DNA-protein cross-links. The various DNA photoproducts differ in their mutagenic potential (IARC 1992). UVR-induced DNA photoproducts cause a variety of cellular responses that contribute to skin cancer. Unrepaired DNA photoproducts may result in the release of cytokines that contribute to tumor promotion, tumor progression, immunosuppression, and the induction of latent viruses (IARC 1992, Yarosh and Kripke 1996).

UVB is considered to be the major cause of skin cancer, despite the fact that it does not penetrate the skin as deeply as UVA or react with the outer skin layer as vigorously as UVC. Its high reactivity with macromolecules, coupled with the depth to which it penetrates skin, makes UVB the most potent portion of the UV spectrum for both short-term and long-term biological effects. UVA, while possibly not as dangerous, also causes biological damage (Farmer and Naylor 1996).

Use

Broad-spectrum UVR has many uses as a natural source of energy and is important in various biological processes. Solar radiation is required for life. Plants must have sunlight to grow and to produce carbohydrates and oxygen. Broad-spectrum UVR from solar radiation helps produce vitamin D in human skin cells. Vitamin D metabolites promote the absorption of calcium by the intestinal tract; therefore, vitamin D is essential for the growth and development of

healthy bones. Brief exposure to sunlight on a regular basis is sufficient to produce all of the vitamin D most people need. This vitamin can also be obtained from dietary sources. Artificial sources of broad-spectrum UVR have many uses, including tanning, medical diagnosis and treatment, and promotion of polymerization reactions (e.g., curing of protective coatings). Sunbeds use artificially produced UVR to enable individuals to develop a suntan for cosmetic reasons. Originally, sunbeds were built with mercury arc lamps, which emitted large quantities of UVB and UVC. Now, sunbeds and solaria emit mostly UVA (IARC 1992).

Broad-spectrum UVR has both diagnostic and therapeutic uses in medicine and dentistry. More than 30 disorders now can be treated through UVA exposure combined with compounds called psoralens (PUVA therapy). Psoriasis and eczema are the skin diseases most frequently treated with PUVA therapy. PUVA can also be used with UVB exposure to treat psoriasis patients who are not good candidates for systemic therapy with methotrexate or etretinate (Morrison 1992). In addition, broad-spectrum UVR and, more commonly, UVB are used with coal-tar creams to treat psoriasis (Reid 1996). UVB also may be used to convert 7-dehydrocholesterol (provitamin D) to vitamin D in the skin of vitamin D-deficient patients.

UVA may be a component of the phototherapy used to treat neonatal jaundice or hyperbilirubinemia. Typically, an infant is irradiated with visible light for several hours a day, for up to one week. However, the lamps also may emit UVR, and one commercial neonatal phototherapy unit was found to emit UVA and shorter wavelengths of UVR (IARC 1992). UVA has been found to react with melatonin, a hormone that helps to regulate sleep-wake cycles. Although the photo-products of melatonin have not been identified, melatonin has been predicted to be moderately phototoxic (Kim *et al.* 1999).

Broad-spectrum UVR has many industrial applications. One of its major industrial uses is in photopolymerization, including curing of protective coatings and inks. Broad-spectrum UVR is used to simulate weathering of various materials, such as polymers. UVR (usually UVC at 260 to 265 nm) is used to sterilize and disinfect tools and materials. UVR is also used in UV photography, UV lasers, and dental examinations to detect early dental caries, dental plaque, and calculus (IARC 1992).

Sources

In the broadest sense, broad-spectrum UVR is formed when something is heated or when electrons that have been raised to an excited state return to a lower energy level. Broad-spectrum UVR is naturally emitted by the sun. An estimated two thirds of the energy emitted by the sun penetrates the atmosphere. Broad-spectrum UVR constitutes approximately 5% of the solar radiation that reaches the earth's surface (IARC 1992).

Six artificial sources of broad-spectrum UVR have been identified: incandescent lights, gas-discharge lamps, arc lamps, fluorescent lamps, metal halide lamps, and electrodeless lamps. Incandescent sources provide visible radiation in a continuous spectrum. Gas-discharge lamps produce visible radiation when an electrical current is passed through a gas. The type of gas present in the lamp determines the emission wavelengths; low gas pressures produce narrow bands, whereas higher pressures produce broad bands. Arc lamps are intense sources of broad-spectrum UVR and often are used to simulate solar radiation. Fluorescent lamps emit radiation from a low-pressure mercury discharge, which produces a strong emission at 254 nm; this radiation excites the phosphor-coated lamp to produce fluorescence. Various emission spectra can be obtained by altering the makeup and thickness of the phosphor and the glass envelope. In metal halide lamps, metal halide salts are added to a mercury-

vapor discharge lamp, thus creating extra emission lines. Electrodeless lamps use magnetrons to generate microwave energy, which then is absorbed by the discharge tube (IARC 1992).

Low-pressure mercury-vapor lamps, sunlamps, and black-light lamps are considered to be low-intensity UVR sources. High-intensity UVR sources include high-pressure mercury-vapor lamps, high-pressure xenon arc lamps, xenon-mercury arc lamps, plasma torches, and welding arcs.

Sunlamps and sunbeds emit broad-spectrum UVR. Sunbeds now chiefly emit UVA; however, before the mid 1970s, they more commonly emitted UVB and UVC (IARC 1992). Three different UVA phosphors have been used in sunlamps sold in the United States since the late 1970s, producing emission spectra that peak at 340, 350, or 366 nm. Two modern sunlamps evaluated by the U.S. Food and Drug Administration emitted 99.0% and 95.7% UVA; the remaining radiation was UVB. A new high-pressure UVA sunbed with eighteen 1,600-watt filtered arc lamps emitted 99.9% UVA. An older type of sunlamp, used prior to the late 1970s (UVB/FS type), emitted 48.7% UVA (Miller *et al.* 1998).

Exposure

The greatest source of human exposure to broad-spectrum UVR is solar radiation; however, the exposure varies with geographical location. Information on global broad-spectrum UVR levels has been compiled from data gathered for epidemiological studies of skin cancer and other health effects, such as premature aging of the skin, cataracts, and suppression of the immune response. Despite the large number of measurements, estimating human exposure is complex. The UVR wavelengths to which an individual is exposed vary considerably with latitude, altitude, time of day, and season. People also vary in their length of outdoor exposure, the parts of the body they expose, and the shapes of their bodies. Nevertheless, many studies have estimated exposure to broad-spectrum UVR. Few studies, however, were able to distinguish between UVA, UVB, and UVC exposure (IARC 1992).

Various factors influence terrestrial levels of UVA (i.e., levels found at the earth's surface). UVA levels decrease with increasing distance from the equator and increase with increasing altitude. Terrestrial UVA levels are also decreased by stratospheric ozone, which varies with latitude and season. When there is less ozone, more UVA reaches the earth's surface. Time of day also influences UVA levels. Clouds reduce the amount of UVA reaching ground level. Air pollution, including tropospheric ozone, can decrease UVA exposure, especially in urban areas. Surface reflection also contributes to personal exposures to UVA and can result in exposure to body parts that otherwise would be shaded from the sun (IARC 1992).

Terrestrial UVB levels are affected by the same factors as terrestrial UVA levels. However, since UVB is absorbed more by stratospheric ozone than is UVA, differences in latitude and altitude affect UVB exposure more than UVA exposure. Seasonal changes affect UVB levels, mostly in temperate regions. Generally, cloud cover scatters less than 10% of the UVB under a clear sky; however, very heavy cloud cover virtually eliminates UVB, even in the summer. Surface reflection also contributes to human UVB exposure (IARC 1992).

Commonly used fluorescent sunlamps deliver 0.3 to 1.2 times the annual UVA dose from the sun to a typical tanner exposed for 20 sessions at 2 minimal erythemal doses (MED) per session (Miller *et al.* 1998). (The MED is the lowest UVR exposure sufficient to produce well-defined reddening of the skin within 24 hours of exposure.) A frequent tanner (100 sessions at 4 MED per session) receives 1.2 to 4.7 times the annual solar UVA dose, while the newer high-pressure sunlamps deliver 12 times the annual solar UVA dose to the frequent

tanner. About 25 million people in the United States use sunbeds each year, and 1 million to 2 million people visit tanning facilities as often as 100 times per year (Sikes 1998, Swerdlow and Weinstock 1998). Teenagers and young adults are prominent among users. A 1995 U.S. survey found that of commercial tanning salon patrons, 8% were 16 to 19 years old, 42% were 20 to 29 years old, and 71% were female (Swerdlow and Weinstock 1998).

Anyone working outside (such as agricultural, construction, or road-work laborers) is occupationally exposed to solar radiation. For a group of more than 800 outdoor workers in the United States at 39° N latitude (the latitude of Philadelphia, Pennsylvania), personal annual exposure of the face was estimated at 30 to 200 MED (Rosenthal *et al.* 1991). However, this estimate may be low, because facial exposure was assumed to be only 5% to 10% of ambient exposure, whereas other data suggest that it could be as high as 20%. Based on this higher estimate, the annual facial exposure doses for these outdoor workers would be 80 to 500 MED (IARC 1992).

Occupational exposure to artificial broad-spectrum UVR occurs in industrial photo processes, principally UV curing of polymer inks, coatings, and circuit board photoresists; sterilization and disinfection; quality assurance in the food industry; medical and dental practices; and welding (IARC 1992). UV lasers, such as those used in cornea shaping and coronary angioplasty, are another potential source of occupational exposure, with relative risks that could be comparable to risks for individuals in outdoor professions (Sternborg *et al.* 1991). Electric arc welders are the largest occupational group with exposure to artificial broad-spectrum UVR. It is estimated that more than 500,000 welders in the United States have been occupationally exposed to broad-spectrum UVR. Occupational exposure to artificial broad-spectrum UVR depends on both the source of exposure and the protective methods used to decrease exposure. Some artificial broad-spectrum UVR sources (such as germicidal lamps in some uses) are self-contained and present no risk to workers. Other occupational uses, such as use of UVR in laboratories, UV photography, and UV lasers, inevitably lead to broad-spectrum UVR exposure, which may include intense short-term exposures (IARC 1992).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

EPA has developed a suite of regulations to protect stratospheric ozone, guarding against increased UVR exposures resulting from its loss.

Food and Drug Administration (FDA)

Performance standards for sunlamps and other devices that emit UVR have been developed. User instructions and warning labels must accompany sunlamps and other devices that emit UVR. Specifications for the use of UVR for processing and treating food have been developed. A warning must be included with products containing coal tar for the control of psoriasis that reads "Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescription drugs unless directed to do so by a doctor."

Occupational Safety and Health Administration (OSHA)

Regulations have been enacted to protect welders and other workers from UVR exposure during welding operations.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit values (TLVs) have been developed for 56 different wavelengths (ranging from 180 to 400 nm) in the UV spectrum. In addition to these TLVs, specific protections for the eye from exposure to UVR in the 315- to 400-nm spectral range have been developed.

National Institute for Occupational Safety and Health (NIOSH)

NIOSH has established technical guidance for using ultraviolet germicidal irradiation (UVGI) systems to help protect health-care workers who may have an occupational risk of tuberculosis infection. It has been recommended that employers reduce worker exposure to UVR through work scheduling, providing shade, and providing information on UVR exposure risks.

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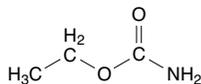
Urethane

CAS No. 51-79-6

Reasonably anticipated to be a human carcinogen

First listed in the *Third Annual Report on Carcinogens* (1983)

Also known as ethyl carbamate or carbamic acid ethyl ester



Carcinogenicity

Urethane is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Urethane caused tumors in several rodent species at several different tissue sites and by several different routes of exposure. It was carcinogenic following administration of a single dose and by prenatal exposure, and neonatal or infant mice generally were more susceptible than adult mice. Malignant and/or benign tumors of the lung, liver, and blood vessels were seen in many studies, along with lymphoma, leukemia, or melanoma (Guyer and Claus 1947, IARC 1974).

Urethane caused benign and/or malignant lung tumors (adenoma or squamous-cell carcinoma) in (1) mice exposed orally (by stomach tube or via the drinking water), by inhalation or intratracheal administration, by intraperitoneal injection, by dermal administration, prenatally, or by lactation, (2) newborn mice exposed by subcutaneous or intraperitoneal injection, (3) hamsters exposed orally or by subcutaneous injection, and (4) newborn hamsters exposed by subcutaneous injection. Urethane caused liver cancer (hepatocellular carcinoma) in (1) adult and newborn mice exposed orally (by stomach tube), by intraperitoneal injection, by subcutaneous injection, and/or prenatally, (2) newborn rats exposed by intraperitoneal injection, (3) female rats exposed orally, and (4) hamsters exposed orally.

Benign and/or malignant blood-vessel tumors (hemangioma or hemangiosarcoma of the liver, spleen, uterus, or unspecified sites) resulted from exposure to urethane via the drinking water in mice and hamsters of both sexes and in female rats. Malignant lymphoma (in some cases of thymic origin) or leukemia resulted from (1) oral exposure (by stomach tube or via the drinking water) in mice and hamsters of both sexes and in female rats and (2) exposure by intraperitoneal injection or subcutaneous injection in newborn mice. In hamsters, melanoma (primarily of the skin) occurred in adults exposed via the drinking water or by subcutaneous injection and in newborns exposed by intraperitoneal or subcutaneous injection. Other types of skin tumors were observed in mice following dermal or oral administration of urethane. In addition, urethane caused tumors at the following tissue sites:

- The mammary gland in female mice, rats, and hamsters exposed orally, female mice exposed dermally, and female rats exposed by intraperitoneal injection.
- The Harderian gland in mice exposed dermally and in newborn mice exposed by intraperitoneal or subcutaneous injection; some tumors were also observed following oral exposure.
- The forestomach in adult hamsters exposed orally and in adult and newborn hamsters exposed by subcutaneous injection.

Tumors were found less consistently in rodents at other tissue sites, including the ovary, Zymbal gland, adrenal cortex of the kidney, and gastrointestinal tract.

Since urethane was listed in the *Third Annual Report on Carcinogens*, additional studies in rodents have been identified. Many of these studies confirmed the findings of the earlier studies or found that urethane caused similar tumors by additional routes of exposure or in additional species. Administration of urethane in the drinking water caused benign and/or malignant tumors of the blood vessels, liver, lung, and Harderian gland in mice of both sexes, the ovary and mammary gland in female mice, and the forestomach and skin in male mice (NTP 2004, Beland 2005). Urethane administered to mice by intraperitoneal injection caused tumors of the thymus (thymoma) in both sexes and the blood vessels in females, in addition to liver and lung tumors, as observed in earlier studies (Dahl *et al.* 1980, Ward *et al.* 1986).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to urethane.

Properties

Urethane is an ester of carbamic acid that exists at room temperature as a colorless or white, almost odorless crystalline solid. It is soluble in water, benzene, alcohol, ether, chloroform, glycerol, and olive oil. Urethane is stable under normal temperatures and pressures (Akron 2009, HSDB 2009). Physical and chemical properties of urethane are listed in the following table.

Property	Information
Molecular weight	89.1 ^a
Specific gravity	0.9813 ^a
Melting point	49°C ^a
Boiling point	185°C ^a
Log K_{ow}	-0.15 ^a
Water solubility	480 g/L at 15°C ^b
Vapor pressure	0.262 mm Hg at 25°C ^a
Vapor density relative to air	3.07 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

The name “urethane” is sometimes applied to high-molecular-weight polyurethanes used as foams, elastomers, and coatings. Such products are not made from the chemical urethane and do not generate it upon decomposition.

Use

The primary use of urethane has been as a chemical intermediate in preparation of amino resins (IARC 1974). The process involves a reaction with formaldehyde to give hydroxymethyl derivatives that are used as cross-linking agents in permanent-press textile treatments designed to impart wash-and-wear properties to fabrics. Urethane is also used as a solubilizer and co-solvent in the manufacture of pesticides, fumigants, and cosmetics, as an intermediate in the manufacture of pharmaceuticals, and in biochemical research (HSDB 2009). Urethane was formerly used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a sclerosing solution for varicose veins, as a hypnotic, and as a topical bactericide. It is also used in veterinary medicine as an anesthetic (IARC 1974). Urethane is produced naturally during many fermentation processes (Zimmerli and Schlatter 1991).

Production

Urethane has been produced commercially in the United States since 1945 (IARC 1974). In 2009, urethane was produced by one manufacturer worldwide, in the United States (SRI 2009), and was available from 21 suppliers, including 13 U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule in 1986 indicated that U.S. production plus imports of urethane totaled 10,000 to 50,000 lb; no inventory update reports have been filed since 1986 (EPA 2004). No data were found on U.S. imports or exports of urethane in 2009.

Exposure

The routes of potential human exposure to urethane are inhalation, ingestion, and dermal contact. Urethane is a naturally occurring substance that is formed during many fermentation processes (Zimmerli and Schlatter 1991). The general population is exposed primarily through ingestion of yeast breads and alcoholic beverages. Measured concentrations of urethane in wine ranged from 8 ng/mL in white table wine to 111 ng/mL in sake (Jagerdeo *et al.* 2002), and urethane concentrations in stone-fruit brandies ranged from 100 to 20,000 µg/kg (ppb) (Zimmerli and Schlatter 1991, Lachenmeier *et al.* 2005). Other alcoholic beverages may contain more urethane than table wine (3 to 9 ppb), including port (16 to 60 ppb), sherry (32 to 242 ppb), and whiskey (68 to 389 ppb) (Brumley *et al.* 1988). Urethane has also been found in dimethyl pyrocarbonate-treated beverages and in beer, orange juice, and some soft drinks (IARC 1974). Other foods with measurable concentrations of urethane include soy sauce, yogurt, and cheese (Zimmerli and Schlatter 1991). Assuming that bread is the major source of urethane intake, the estimated mean intake of urethane in adults is 10 to 20 ng/kg of body weight. Toasting bread increases its urethane concentration 2- to 3-fold. Adding a cup (200 to 300 mL) of table wine to the daily diet could as much as triple urethane intake, and drinking one ounce of cherry or plum brandy could increase daily intake 60 fold over the baseline intake from other food sources. Urethane is also a natural constituent of tobacco and is present in tobacco smoke. Consumers were also potentially exposed to urethane residues in urethane-treated textiles (IARC 1974).

In the 1940s and 1950s, patients with leukemia, multiple myeloma, and mycosis fungoides were treated with urethane, and urethane was measured in the blood of two leukemia patients at concentrations ranging from 4 to 38 mg/100 mL (Archer *et al.* 1948, Kennedy *et al.* 1950, Skipper *et al.* 1951, Seibert *et al.* 1966). Individuals potentially were exposed to urethane in other pharmaceutical products administered by injection (HSDB 2009). Certain patients with epilepsy potentially were exposed to urethane as a contaminant in the anti-convulsant drugs trimethadione and paramethadione. Although one product containing trimethadione is still approved by the U.S. Food and Drug Administration, all three products containing paramethadione have been discontinued (FDA 2009).

According to EPA's Toxics Release Inventory, environmental releases of urethane decreased from 146,500 lb in 1988 to 500 lb in 1997, increasing to 128,000 lb in 2003. In 2007, eight facilities released about 95,000 lb of urethane. Since 1997, most releases of urethane have been to landfills (TRI 2009). In the atmosphere, urethane will exist in the vapor state and react with photochemically produced hydroxyl radicals, with an estimated half-life of 17 hours. If released to soil or water, urethane is expected to adsorb weakly to soil and primarily to leach to groundwater. (HSDB 2009).

Occupational exposure to urethane may occur during its production or its use in medical research. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 9,459

workers, including 5,050 women, potentially were exposed to urethane (NIOSH 1990).

Regulations

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act
Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Listed Hazardous Waste: Waste code for which the listing is based wholly or partly on the presence of urethane = U238.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Urethane has been withdrawn from the market as a pharmaceutical because it was found to be unsafe or not effective, and it cannot be compounded.

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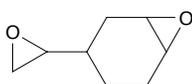
4-Vinyl-1-cyclohexene Diepoxide

CAS No. 106-87-6

Reasonably anticipated to be a human carcinogen

First listed in the *Seventh Annual Report on Carcinogens* (1994)

Also known as 4-vinylcyclohexene diepoxide, 4-vinylcyclohexene dioxide, or 1-epoxyethyl-3,4-epoxycyclohexane



Carcinogenicity

4-Vinyl-1-cyclohexene diepoxide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Dermal exposure to 4-vinyl-1-cyclohexene diepoxide caused tumors in two rodent species and at two different tissue sites. It caused skin cancer (squamous-cell carcinoma) in rats and mice of both sexes and increased the combined incidence of benign and malignant basal-cell skin tumors (adenoma and carcinoma) in rats of both sexes; the predominant skin tumor observed in rats was squamous-cell carcinoma. In female mice, 4-vinyl-1-cyclohexene diepoxide also caused ovarian tumors, which are uncommon in rodents; it increased the combined incidence of benign and malignant granulosa-cell tumors, luteoma, and benign mixed ovarian tumors, and a few of the malignant tumors metastasized to the lung (IARC 1976, 1994, NTP 1989).

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to 4-vinyl-1-cyclohexene diepoxide.

Properties

4-Vinyl-1-cyclohexene diepoxide is a colorless liquid at room temperature (NTP 1989). It is soluble in water; however, it slowly hydrolyzes in aqueous solutions (Akron 2009). Physical and chemical properties of 4-vinyl-1-cyclohexene diepoxide are listed in the following table.

Property	Information
Molecular weight	140.2 ^a
Specific gravity	1.0986 at 20°C/20°C ^a
Melting point	< -55°C ^a
Boiling point	227°C at 760 mm Hg ^a
Log <i>K</i> _{ow}	0.44 ^b
Water solubility	35.2 g/L at 25°C ^b
Vapor pressure	1.17 mm Hg at 25°C ^b

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

4-Vinyl-1-cyclohexene diepoxide is used as a reactive diluent for other diepoxides and for certain epoxy resins derived from bisphenol A and epichlorohydrin (NTP 1989). The epoxy resins are used for embedding samples for electron microscopy (IARC 1994). 4-Vinyl-1-cyclohexene is also used as a chemical intermediate in condensation reactions with dicarboxylic acids, as a monomer for preparation of polyglycols containing epoxy groups, and for homopolymerization to a three-dimensional resin.

Production

In 1989, one company was identified as the major U.S. manufacturer of 4-vinyl-1-cyclohexene diepoxide (NTP 1989). In 2009, no commercial producers of 4-vinyl-1-cyclohexene were identified worldwide, but it was available from twelve suppliers, including eight U.S. suppliers (ChemSources 2009). Reports filed under the U.S. Environmental Protection Agency's Toxic Substances Control Act Inventory Update Rule in 1986 and 1990 indicated that U.S. production plus imports of 4-vinyl-1-cyclohexene diepoxide totaled 10,000 to 500,000 lb (EPA 2004); no inventory update reports have been filed for 4-vinyl-1-cyclohexene diepoxide since 1990.

Exposure

The primary route of potential human exposure to 4-vinyl-1-cyclohexene diepoxide is by inhalation or dermal contact. Workers may be exposed during the manufacture and use of 4-vinyl-1-cyclohexene diepoxide or epoxy-based polyglycols and resins prepared with this chemical (IARC 1994). Laboratory workers may be exposed during preparation of epoxy resin tissue-embedding agents for electron microscopy. The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 6,224 workers, including 1,718 women, potentially were exposed to 4-vinyl-1-cyclohexene diepoxide (NIOSH 1990).

Regulations

No regulations specific to reduction of exposure to 4-vinyl-1-cyclohexene diepoxide were identified.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 10 ppm (60 mg/m³).

Listed as a potential occupational carcinogen.

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Vinyl Halides (Selected)

Introduction

Vinyl bromide, vinyl chloride, and vinyl fluoride belong to a class of structurally related chemicals referred to as “simple vinyl halides” or “halogenated olefins.” These three vinyl halides are listed in the Report on Carcinogens as individual chemicals and not as a class. (The class also includes vinyl iodide, which is not listed in the Report on Carcinogens.) Vinyl chloride was first listed in the *First Annual Report on Carcinogens* (1980) as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, and vinyl bromide and vinyl fluoride were first listed in the *Tenth Report on Carcinogens* (2002) as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals.

The three listed vinyl halides have widespread industrial use, especially in the plastics industry, and the primary route of occupational exposure is inhalation. Numerous epidemiological studies of occupational exposure have shown that vinyl chloride causes cancer of the blood vessels of the liver (hepatic angiosarcoma) in humans (IARC 2008a,b,c). Hepatic angiosarcoma is a very rare type of cancer; its estimated incidence in the United States is only 25 cases per year (Molina and Hernandez 2003). In experimental animals, this type of cancer is usually referred to as hemangiosarcoma; all three listed vinyl halides cause hemangiosarcoma of the liver in experimental animals. No epidemiological studies of the carcinogenicity of vinyl bromide or vinyl fluoride have been identified. However, all three listed vinyl halides are metabolized to similar DNA-reactive intermediates (haloethylene oxide and haloacetaldehyde) via a human cytochrome P450 2E1-dependent pathway and cause genetic damage *in vivo* and *in vitro*. Furthermore, the DNA adducts formed are the same for all three of these vinyl halides, and the etheno adducts can cause DNA miscoding by modifying base-pairing sites (IARC 2008a,b,c). The fact that vinyl bromide, vinyl chloride, and vinyl fluoride all cause hemangiosarcoma of the liver in experimental animals and induce the formation of similar DNA adducts suggests a common mechanism of carcinogenicity for these three vinyl halides.

References

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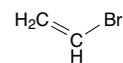
Molina E, Hernandez A. 2003. Clinical manifestations of primary hepatic angiosarcoma. *Dig Dis Sciences* 48(4): 677-682.

Vinyl Bromide

CAS No. 593-60-2

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)



Carcinogenicity

Vinyl bromide is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to vinyl bromide by inhalation caused tumors at several different tissue sites in rats. In rats of both sexes, it caused cancer of the blood vessels of the liver (hepatic hemangiosarcoma), Zymbal-gland cancer (carcinoma), and benign and malignant liver tumors (hepatocellular adenoma and carcinoma) (Benya *et al.* 1982, IARC 1986).

Studies on Mechanisms of Carcinogenesis

Vinyl bromide was genotoxic in *Salmonella typhimurium* (IARC 1986) and *Drosophila melanogaster* (Balling *et al.* 1996) and caused DNA damage in several organs of mice (Sasaki *et al.* 1998). Vinyl bromide is metabolized in a manner similar to vinyl fluoride and vinyl chloride: oxidation via cytochrome P450 to bromoethylene oxide, followed by rearrangement to 2-bromoacetaldehyde, which is oxidized to bromoacetic acid. Vinyl bromide is metabolized more slowly than vinyl chloride (by about an order of magnitude) (Bolt *et al.* 1978), which suggests that vinyl bromide's greater carcinogenic potency may be related to kinetic differences in metabolism. Vinyl bromide appears to be a more potent inducer of hepatic hemangiosarcoma in rats than is vinyl chloride.

Vinyl bromide metabolites bind covalently to DNA and to protein; 2-bromoethylene oxide is the major DNA binding agent, and 2-bromoacetaldehyde is the major protein alkylating agent (Guengerich *et al.* 1981). After exposure to vinyl chloride, the major DNA adduct formed is 7-(2-oxoethyl)guanine (constituting approximately 98% of all adducts). By analogy, the 7-position of guanine is considered to be the preferred site of DNA alkylation by bromoethylene oxide, the primary metabolite of vinyl bromide (Bolt 1988). Chloroacetaldehyde and bromoacetaldehyde can react with adenine or cytosine bases in DNA or RNA to produce cyclic etheno-DNA- and -RNA adducts (1,N⁶-ethenoadenosine and 3,N⁴-ethenocytosine). Etheno-DNA adducts can cause DNA miscoding by modifying base-pairing sites. Because the cyclic etheno adducts have a longer half-life than does 7-(2-oxoethyl)guanine, they have a greater potential to accumulate with long-term exposure (Swenberg *et al.* 1992). The mechanism of carcinogenicity of vinyl bromide may be similar to that of vinyl chloride (see Introduction). There is no evidence to suggest that mechanisms by which vinyl bromide causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to vinyl bromide.

Properties

Vinyl bromide is a halogenated olefin compound that exists at room temperature as a colorless gas with a characteristic pungent, but pleas-

ant, odor. It is insoluble in water but soluble in ethanol, ether, acetone, chloroform, and benzene. It is stable under normal temperatures and pressures, but is extremely flammable (Akron 2009). Physical and chemical properties of vinyl bromide are listed in the following table.

Property	Information
Molecular weight	106.9 ^a
Specific gravity	1.4933 at 20°C ^a
Melting point	-137.8°C ^a
Boiling point	15.8°C at 760 mm Hg ^a
Log K_{ow}	1.57 ^a
Water solubility	7.600 g/L at 25°C ^b
Vapor pressure	1,033 mm Hg at 25°C ^a
Vapor density relative to air	3.7 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Vinyl bromide is used primarily in the production of polymers and copolymers. It is used in polymers as a flame retardant and in the production of monoacrylic fibers for carpet-backing material. Combined with acrylonitrile as a co-monomer, it is used to produce fabrics and fabric blends used in sleepwear (mostly children's) and home furnishings. When copolymerized with vinyl acetate and maleic anhydride, vinyl bromide is used to produce granular products. Copolymers of vinyl chloride and vinyl bromide are used to prepare films, for impregnating or laminating fibers, and as rubber substitutes. Vinyl bromide also is used in leather and fabricated-metal products. Polyvinyl bromide, made from vinyl bromide, is a polymer of little commercial value, because it is unstable at room temperature. Vinyl bromide is also used in the production of pharmaceuticals and fumigants (IARC 1986).

Production

Vinyl bromide was first produced in the United States in 1968. In 1982, U.S. production was estimated at 51 million pounds. Vinyl bromide was not listed by the U.S. Environmental Protection Agency as a high-production-volume chemical in 1994, indicating that annual production was less than 1 million pounds (EPA 1994). In 2009, one U.S. manufacturer of vinyl bromide was identified (HSDB 2009).

Exposure

The main routes of potential exposure to vinyl bromide are inhalation and dermal contact. Vinyl bromide is not known to occur naturally in the environment, and it is assumed that most, if not all, exposure of the general population occurs as a result of industrial contamination of the environment (IARC 1986). According to EPA's Toxics Release Inventory, environmental releases of vinyl bromide between 1988 and 1997 and ranged from 1,600 lb to almost 55,000 lb. No releases were reported in 1998, and no releases have been reported since 1999, when one facility released 500 lb to air (TRI 2009).

Workers in the following industries potentially are exposed to vinyl bromide: Chemicals and Allied Production, Rubber and Plastic Production, Leather and Leather Product Production, and Fabricated Metal Production for Wholesale Trade (NIOSH 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 1,821 workers potentially were exposed to vinyl bromide (NIOSH 1990). Occupational exposure to vinyl bromide (median 8-h time-weighted average) calculated for a vinyl bromide manufacturing plant ranged from 0.4 to 27.5 mg/m³ (0.1 to 6.3 ppm), depending on the job and the area surveyed. Concentrations in one-hour personal air samples were 0.4 to 1.7 mg/m³ (0.09 to 0.4 ppm) for a plant operator, 1.3 to 2.2 mg/m³ (0.3 to 0.5 ppm) for a laboratory techni-

cian, and 5.2 to 27.5 mg/m³ (1.2 to 6.3 ppm) for two loading crewmen (IARC 1986).

Regulations

Department of Transportation (DOT)

Vinyl bromide is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 100 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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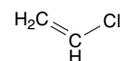
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Vinyl Chloride

CAS No. 75-01-4

Known to be a human carcinogen

First listed in the *First Annual Report on Carcinogens* (1980)



Carcinogenicity

Vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

The strongest evidence that vinyl chloride causes cancer in humans is based on numerous epidemiological studies and case reports that show its association with cancer of the blood vessels of the liver (hepatic angiosarcoma), which is a very rare tumor. Several studies have also reported that exposure to vinyl chloride causes cancer at other tissue sites, including the liver (hepatocellular carcinoma), brain, lung, lymphatic system, and hematopoietic system (IARC 1987).

Since vinyl chloride was listed in the *First Annual Report on Carcinogens*, epidemiological studies have continued to provide strong evidence for an association between vinyl chloride exposure and hepatic angiosarcoma (IARC 2008). As of 1999, 197 cases of vinyl chloride-associated hepatic angiosarcoma had been reported, including 50 in the United States (Kielhorn *et al.* 2000). Two studies also found that the risk of liver cancer (hepatocellular carcinoma) increased with increasing cumulative exposure to vinyl chloride. Some studies also reported an excess of cancer of the connective and soft tissues. An excess of brain cancer was found in some but not all studies; significantly increased risks were found among exposed workers with the highest durations of exposure or who worked in plants that had begun production earlier. However, risk estimates did not increase with increasing measures of cumulative exposure, duration of exposure, or time since first exposure. The results of recent studies on lung cancer, lymphoma, and leukemia and vinyl chloride exposure were conflicting (IARC 2008).

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of vinyl chloride in experimental animals. Vinyl chloride caused tumors in three rodent species, at different several tissue sites, and by several different routes of exposure (IARC 1979). In several studies, vinyl chloride caused tumors of the blood vessels of the liver (hepatic hemangiosarcoma) in mice and rats exposed by inhalation and in rats exposed orally. Inhalation exposure to vinyl chloride also caused mammary-gland tumors in rats, mice, and hamsters; skin tumors in rats and hamsters; Zymbal-gland tumors in rats; and lung tumors in mice. Zymbal-gland cancer (carcinoma) was also observed in prenatally exposed rats. Combined inhalation exposure to vinyl chloride and oral exposure to ethanol caused more liver tumors (including angiosarcoma) than did exposure to vinyl chloride alone.

Since vinyl chloride was listed in the *First Annual Report on Carcinogens*, additional studies in rodents have been identified. Vinyl chloride administered by additional routes of exposure—perinatal (for 5 weeks beginning at birth) and prenatal followed by inhalation exposure (for 8 or 69 weeks)—also caused hepatic hemangiosarcoma (IARC 2008). Other studies reported that exposure to vinyl chloride caused tumors at additional tissue sites. Inhalation exposure to vinyl chloride caused hemangiosarcoma not only in the liver, but at sites other than the liver in rats, mice, and hamsters. Inhalation exposure also caused stomach tumors (adenoma) in hamsters and nasal and kidney tumors in rats. Liver cancer (hepatocellular carcinoma) was observed in rats after inhalation exposure, perinatal exposure, or prenatal exposure followed by inhalation exposure.

Studies on Mechanisms of Carcinogenesis

Vinyl chloride is metabolized by cytochrome P450 enzymes to form chloroethylene oxide, which can undergo spontaneous rearrangement to form chloroacetaldehyde; both of these metabolites can bind

to DNA. One major DNA adduct, 7-(2'-oxoethyl)guanine, and four minor adducts (etheno adducts) have been identified. The etheno adducts (but not the major adduct) cause mutations, mainly base-pair substitutions and, to a lesser degree, frameshift mutations. Mutations were detected in the *p53* tumor-suppressor gene and the *ras* proto-oncogene in angiosarcomas from humans and angiosarcomas of the liver or hepatocellular carcinomas from rats exposed to vinyl chloride. Most of the mutations occurred at A:T base pairs, which is consistent with the mutagenic properties of the etheno adducts (especially the 1,N⁶-ethenoadenine adduct) (Kielhorn *et al.* 2000).

Vinyl chloride caused genetic damage in many test systems, including bacteria, yeast, insects, cultured human and other mammalian cells, and rodents exposed *in vivo*, and in exposed humans. The genetic damage included mutations, DNA damage, micronucleus formation, chromosomal aberrations, and sister chromatid exchange. Vinyl chloride caused mutations in bacteria with or without metabolic activation (addition of rodent liver microsomes to simulate mammalian metabolism); however, its metabolites chloroethylene oxide and chloroacetaldehyde were more potent mutagens than vinyl chloride. These results suggest that vinyl chloride may require mammalian metabolic activation in order to cause genetic damage in other test systems (Giri 1995).

Properties

Vinyl chloride is a halogenated olefin compound that exists at room temperature as a colorless gas with an ethereal odor. It is slightly soluble in water and soluble in most organic solvents, including alcohol, ether, benzene, carbon tetrachloride and other chlorinated solvents, hydrocarbons, and oils. It is very flammable and polymerizes in light or the presence of a catalyst (IARC 1979). Physical and chemical properties of vinyl chloride are listed in the following table.

Property	Information
Molecular weight	62.5 ^a
Specific gravity	0.9106 at 20°C/4°C ^a
Melting point	-153.7°C ^a
Boiling point	-13.3°C ^a
Log <i>K</i> _{ow}	1.62 ^b
Water solubility	8.8 g/L at 25°C ^b
Vapor pressure	2980 mm Hg at 25°C ^a
Vapor density relative to air	2.15 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Vinyl chloride is used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC) and copolymers. PVC is a plastic resin used in many consumer and industrial products, including automotive parts and accessories, furniture, medical supplies, containers, wrapping film, battery cell separators, electrical insulation, water-distribution systems, flooring, windows, videodiscs, irrigation systems, and credit cards. More than 95% of all vinyl chloride monomer produced is used to make PVC and its copolymers; the rest is used in organic synthesis and miscellaneous applications (Kielhorn *et al.* 2000, HSDB 2009). Vinyl chloride-vinyl acetate copolymers are used extensively to produce films and resins (IARC 1974, 1979, NCI 1978, ATSDR 2006). Vinyl chloride previously was used as a refrigerant, as an extraction solvent, and in aerosol propellants, but these uses were banned in 1974 because of vinyl chloride's carcinogenic effects (HSDB 2009).

Production

Vinyl chloride was first produced commercially in the 1920s and is now one of the highest-volume chemicals produced in the United

States. Annual U.S. production increased from 6 billion to 9 billion pounds in the late 1970s through the 1980s to 15 billion pounds in the mid 1990s (Kirschner 1996, HSDB 2009). Among chemicals produced in the United States, vinyl chloride ranked 18th in production volume in 1995 and 17th in 1994 (Kirschner 1996). In 2000, the production capacity for vinyl chloride was reported to be 17.6 billion pounds (CMR 2000). In 2009, thirteen U.S. producers (SRI 2009) and eight U.S. suppliers of vinyl chloride were identified (ChemSources 2009). U.S. imports of vinyl chloride reached a peak of 302 million pounds in 1989. Imports have fluctuated and then declined since then and were 818,000 pounds in 2009 (ATSDR 2006, USITC 2009). From the late 1970s to the mid 1990s, annual U.S. exports of vinyl chloride fluctuated between 685 million pounds and 2.2 billion pounds (ATSDR 2006, HSDB 2009). Exports were 1.03 billion kilograms (2.3 billion pounds) in 2000 and 930 million kilograms (2.1 billion pounds) in 2009 (USITC 2009).

Exposure

The general population potentially is exposed to vinyl chloride through inhalation of contaminated air, ingestion of contaminated drinking water and foods, or dermal contact with consumer products. However, the exposure levels for the majority of the population are very low (Kielhorn *et al.* 2000, ATSDR 2006, HSDB 2009). In the past, vinyl chloride was detected in various foods and beverages that were packaged in materials made of PVC; however, U.S. Food and Drug Administration regulations have essentially eliminated this route of exposure. The estimated average daily intake of vinyl chloride from the diet is essentially zero (ATSDR 2006). Vinyl chloride has also been detected in domestic and foreign cigarettes and little cigars at levels ranging from 5.6 to 27 ng per cigarette and in a marijuana cigarette at 5.4 ng (IARC 1979).

Vinyl chloride is released into the environment in emissions and effluents from the plastics industry (ATSDR 2006). According to the U.S. Environmental Protection Agency's Toxics Release Inventory, annual environmental releases of vinyl chloride declined slowly from 1.4 million pounds in 1988 to less than 1 million pounds since 1998. In 2007, 43 facilities released 373,000 lb of vinyl chloride, mostly to air (TRI 2009). Segments of the general population living near emission sources potentially are exposed to relatively high levels of vinyl chloride in air. Concentrations in the air near emission sources ranged from trace levels to over 2,600 $\mu\text{g}/\text{m}^3$, and the average daily intake of vinyl chloride by residents living near emission sources ranged from trace amounts to 2,100 μg . Ambient air in rural and urban areas of the United States typically does not contain detectable levels of vinyl chloride. The majority of the population is not expected to be exposed to vinyl chloride in drinking water. Only 7 of 945 water supplies sampled throughout the United States contained detectable levels of vinyl chloride. In another study, vinyl chloride was detected in only 12 of 11,202 public water supplies using surface waters as their primary source. EPA estimated that about 0.9% of the U.S. population was exposed to vinyl chloride in drinking water at concentrations of 1.0 $\mu\text{g}/\text{L}$ or higher and that 0.3% was exposed at concentrations higher than 5 $\mu\text{g}/\text{L}$ (ATSDR 2006).

Potential routes of occupational exposure to vinyl chloride are inhalation and dermal contact. Occupational exposure generally occurs after production, when the finished monomer is piped to storage or transportation, or during maintenance. The potential for exposure is high during the process of polymerization to form PVC resins or other materials, because vinyl chloride monomer may escape into the air (NCI 1978). The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that 81,314 workers potentially were exposed to vinyl chloride (ATSDR 2006).

Regulations

Consumer Product Safety Commission (CPSC)

Self-pressurized products intended for household use that contain vinyl chloride are banned.

Department of Transportation (DOT)

Vinyl chloride is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

National Emissions Standards for Hazardous Air Pollutants: Listed as a hazardous air pollutant.

New Source Performance Standards: Manufacture of vinyl chloride is subject to certain provisions for the control of volatile organic compound emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Urban Air Toxics Strategy: Identified as one of 33 hazardous air pollutants that present the greatest threat to public health in urban areas.

Clean Water Act

Effluent Guidelines: Listed as a toxic pollutant.

Water Quality Criteria: Based on fish or shellfish and water consumption = 2.0 $\mu\text{g}/\text{L}$; based on fish or shellfish consumption only = 530 $\mu\text{g}/\text{L}$.

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable quantity (RQ) = 1 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements.

Resource Conservation and Recovery Act

Characteristic Hazardous Waste: Toxicity characteristic leaching procedure (TCLP) threshold = 0.2 mg/L.

Listed Hazardous Waste: Waste codes for which the listing is based wholly or partly on the presence of vinyl chloride = U043, K019, K020, K028, K029.

Listed as a hazardous constituent of waste.

Safe Drinking Water Act

Maximum contaminant level (MCL) = 0.002 mg/L.

Food and Drug Administration (FDA)

Maximum permissible level in bottled water = 0.002 mg/L.

Aerosol drug products containing vinyl chloride have been withdrawn from the market and may not be compounded, because vinyl chloride was found to be unsafe or not effective.

Vinyl chloride is banned from use in cosmetic aerosol products.

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers.

Permissible exposure limit (PEL) = 1 ppm.

Ceiling concentration = 5 ppm (15 min).

Comprehensive standards have been developed for occupational exposure to vinyl chloride.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Listed as a potential occupational carcinogen.

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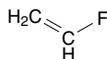
Vinyl Fluoride

CAS No. 75-02-5

Reasonably anticipated to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Also known as fluoroethene



Carcinogenicity

Vinyl fluoride is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.

Cancer Studies in Experimental Animals

Exposure to vinyl fluoride by inhalation caused tumors at several different tissue sites in rats and mice. In rats and mice of both sexes, it caused cancer of the blood vessels of the liver (hepatic hemangiosarcoma). In rats of both sexes, it also caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) and cancer of the Zymbal gland (carcinoma). In mice, it also caused benign or malignant lung tumors (bronchiolar/alveolar adenoma or adenocarcinoma) and benign Harderian-gland tumors (adenoma) in both sexes and mammary-gland cancer (adenocarcinoma) in females (Bogdanffy *et al.* 1995, IARC 1995).

Studies on Mechanisms of Carcinogenesis

Vinyl fluoride caused mutations in *Salmonella typhimurium* in the presence of mammalian metabolic activation. It also caused gene mutations and chromosomal aberrations in Chinese hamster ovary cells (with metabolic activation), sex-linked recessive lethal mutations in *Drosophila melanogaster*, and micronucleus formation in bone-marrow cells of female mice (IARC 1995).

Vinyl fluoride likely is metabolized in a manner similar to vinyl chloride: oxidation via cytochrome P450 to fluoroethylene oxide, followed by rearrangement to 2-fluoroacetaldehyde, which is oxidized to fluoroacetic acid. Human, rat, and mouse liver microsomes metabolize vinyl fluoride at similar rates (Cantoreggi and Keller 1997). Vinyl fluoride metabolites form covalent DNA adducts. Inhalation exposure of rats and mice to vinyl fluoride caused a dose-related increase in the formation of the promutagenic adduct *N*²,3-ethenoguanine in liver DNA (Swenberg *et al.* 1995). The mechanism of carcinogenicity of vinyl fluoride may be similar to that of vinyl chloride (see Intro-

duction). There is no evidence to suggest that mechanisms by which vinyl fluoride causes tumors in experimental animals would not also operate in humans.

Cancer Studies in Humans

No epidemiological studies have evaluated the relationship between human cancer and exposure specifically to vinyl fluoride.

Properties

Vinyl fluoride is a halogenated olefin compound that exists at room temperature as a colorless gas with a faint ethereal odor. It is slightly soluble in water, and soluble in alcohol, ether, and acetone. It polymerizes freely and forms explosive mixtures with air (IARC 1986). Physical and chemical properties of vinyl fluoride are listed in the following table.

Property	Information
Molecular weight	46.0 ^a
Specific gravity	0.636 (liquid) at 21°C ^a
Melting point	-160.5°C ^a
Boiling point	-72°C ^a
Log <i>K</i> _{ow}	1.19 ^a
Water solubility	12.9 g/L at 25°C ^b
Vapor pressure	0.414 mm Hg at 25°C ^a
Vapor density relative to air	1.58 ^a

Sources: ^aHSDB 2009, ^bChemIDplus 2009.

Use

Vinyl fluoride is used primarily in the production of polyvinyl fluoride and other fluoropolymers. Polymers of vinyl fluoride are resistant to weather and exhibit great strength, chemical inertness, and low permeability to air and water. Polyvinyl fluoride is laminated with aluminum, galvanized steel, and cellulose materials and is used as a protective surface for the exteriors of residential and commercial buildings. Polyvinyl fluoride laminated with various plastics has been used to cover walls, pipes, and electrical equipment and inside aircraft cabins (IARC 1995).

Production

Vinyl fluoride was first prepared in the early 1900s by reaction of zinc with 1,1-difluoro-2-bromoethane. Modern preparation of vinyl fluoride involves reaction of acetylene and hydrogen fluoride in the presence of a mercury-based or aluminum-based catalyst (IARC 1995). Annual U.S. production of vinyl fluoride was 3.3 million pounds in the 1970s (HSDB 2009). The U.S. Environmental Protection Agency listed vinyl fluoride as a high-production-volume chemical in 1990, indicating that annual production exceeded 1 million pounds (EPA 2006). In 2009, only one U.S. manufacturer of vinyl fluoride was identified (HSDB 2009).

Exposure

Exposure to vinyl fluoride in the environment will occur by inhalation, because vinyl fluoride is released into the environment as a gas (IPCS 1993). Occupational exposure to vinyl fluoride also occurs primarily by inhalation (HSDB 2009). Skin and eye contact can occur among workers handling liquid vinyl fluoride. Handling of liquid vinyl fluoride also would cause frostbite (IPCS 1993). Occupational exposure to vinyl fluoride was studied in a manufacturing and polymerization facility in the United States. In eight personal air samples taken at the manufacturing facility, concentrations of vinyl fluoride generally were less than 2 ppm (3.76 mg/m³). In one personal sample, however, the concentration was 21 ppm (39.5 mg/m³). Vinyl fluoride concentrations in seven personal samples taken in the polymerization facility

ranged from 1 to 4 ppm (1.88 to 7.52 mg/m³). In four general working areas, the vinyl fluoride concentrations ranged from 1 to 5 ppm (1.88 to 9.4 mg/m³) (IARC 1995).

Regulations

Department of Transportation (DOT)

Vinyl fluoride is considered a hazardous material, and special requirements have been set for marking, labeling, and transporting this material.

Environmental Protection Agency (EPA)

Clean Air Act

Prevention of Accidental Release: Threshold quantity (TQ) = 10,000 lb.

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 1 ppm.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 ppm.

Ceiling recommended exposure limit = 5 ppm.

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Wood Dust

CAS No.: none assigned

Known to be a human carcinogen

First listed in the *Tenth Report on Carcinogens* (2002)

Carcinogenicity

Wood dust is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.

Cancer Studies in Humans

Many case reports and epidemiological studies (including cohort studies and case-control studies that specifically addressed nasal cancer) have found a strong association between exposure to wood dust and cancer of the nasal cavity. Strong and consistent associations with cancer of the nasal cavity and paranasal sinuses were observed both in studies of people whose occupations were associated with wood-dust exposure and in studies that directly estimated wood-dust exposure. Cancer risks were highest for adenocarcinoma, particularly among European populations. Studies of U.S. populations showed similar significant positive associations between wood-dust exposure and adenocarcinoma of the nasal cavity. A pooled analysis

of 12 case-control studies found a very high estimated relative risk of adenocarcinoma (45.5) among men with the greatest exposure, and the risk increased with increasing duration of exposure (Demers *et al.* 1995). The association between wood-dust exposure and elevated risk of nasal cancer (adenocarcinoma) in a large number of independent studies and in many different occupations in many countries strongly supports the conclusion that the increased risk is due to wood-dust exposure, rather than to simultaneous exposure to other substances, such as formaldehyde or wood preservatives (IARC 1995, NTP 2000).

Other types of nasal cancer (squamous-cell carcinoma of the nasal cavity) and cancer at other tissue sites, including cancer of the nasopharynx and larynx and Hodgkin's disease, have been associated with exposure to wood dust in several epidemiological studies. However, these associations were not found in all studies, and the overall epidemiological evidence is not strong enough or consistent enough to allow firm conclusions to be drawn about the role of wood-dust exposure in the development of cancer at tissue sites other than the nasal cavity (IARC 1995, NTP 2000).

Studies on Mechanisms of Carcinogenesis

Polar organic solvent extracts of some hardwood dusts were weakly mutagenic in *Salmonella typhimurium*, and two chemicals found in wood, delta-3-carene and quercetin, also were mutagenic in *S. typhimurium*. *In vivo* exposure of mammals and *in vitro* exposure of mammalian cells to organic solvent extracts of some wood dusts (beech and oak) caused DNA damage, micronucleus formation, and chromosomal aberrations (primarily chromatid breaks). Elevated rates of DNA damage (primarily single-strand breaks and DNA repair) and micronucleus formation were observed in peripheral-blood lymphocytes from people occupationally exposed to wood dust (IARC 1995, NTP 2000).

The roles of specific chemicals found in wood dust (either naturally in the wood or added to it in processing) in causing cancer are not clear. The particulate nature of wood dust also may contribute to wood-dust-associated carcinogenesis, because a high proportion of dust particles generated by woodworking typically are deposited in the nasal cavity. Some studies of people with long-term exposure to wood dust have found decreased mucociliary clearance and enhanced inflammatory reactions in the nasal cavity. Also, cellular changes (metaplasia and dysplasia) observed in the nasal mucosa of woodworkers and of laboratory animals may be precancerous (IARC 1995, NTP 2000).

Cancer Studies in Experimental Animals

The evidence from studies in experimental animals is inadequate to evaluate the carcinogenicity of wood dust. No tumors attributable to beech wood-dust exposure were found in rats exposed by inhalation or intraperitoneal injection. Inhalation exposure to wood dust also did not significantly affect the incidence of tumors caused by simultaneous exposure to other compounds (known to be carcinogenic in humans or experimental animals), including formaldehyde or sidestream cigarette smoke in rats and *N*-nitrosodiethylamine in hamsters. However, each of these studies was limited by such factors as small numbers of animals or exposure groups, short study duration, or inadequate data reporting. In female mice, dermal exposure to a methanol extract of beech wood dust resulted in significant dose-related increases in the incidence of skin tumors (squamous-cell papilloma and carcinoma) and mammary-gland tumors (adenocarcinoma, adenoacanthoma, and mixed tumors) (IARC 1995).

Properties

Wood is an important worldwide renewable natural resource. Forests cover about one third of the earth's total land mass (about 3.4 million square kilometers). An estimated 12,000 species of trees each produce a characteristic type of wood, and the species of trees harvested vary considerably among different countries and even among different regions of a country. However, even in countries with high domestic production of wood, some wood may be imported for specific uses, such as furniture production (IARC 1995).

Most of the 12,000 tree species are broad-leaved deciduous trees, or hardwoods, principally angiosperms. Only about 800 species are pines, firs, and other coniferous trees, or softwoods, principally gymnosperms. The terms "hardwood" and "softwood" refer to the species, and not necessarily the hardness of the wood. Although hardwoods generally are denser than softwoods, the density varies greatly within each group, and the hardness of the two groups overlaps somewhat. The composition of softwood tissue is simpler than that of hardwood, consisting of mainly one type of cells, tracheids. Hardwoods show more detailed differentiation among stabilizing, conducting, and storage tissue. Although most trees harvested worldwide are hardwoods (58% of volume), much of the hardwood is used for fuel. Softwood is the major wood used for industrial purposes (69%); however, the percentage varies from region to region (IARC 1995).

Wood dust is a complex mixture generated when timber is processed, such as when it is chipped, sawed, turned, drilled, or sanded. Its chemical composition depends on the species of tree and consists mainly of cellulose, polyoses, and lignin, plus a large and variable number of substances with lower relative molecular mass. Cellulose is the major component of both softwood and hardwood. Polyoses (hemicelluloses), which consist of five neutral sugar units, are present in larger amounts in hardwood than in softwood. The lignin content of softwood is higher than that of hardwood. The lower-molecular-mass substances significantly affect the properties of wood; these include substances extracted with nonpolar organic solvents (fatty acids, resin acids, waxes, alcohols, terpenes, sterols, steryl esters, and glycerols), substances extracted with polar organic solvents (tannins, flavonoids, quinones, and lignans), and water-soluble substances (carbohydrates, alkaloids, proteins, and inorganic material). Wood dust is also characterized by its moisture content: "dry" wood has a moisture content of less than approximately 15%, and "moist" wood has a higher moisture content. Woodworking operations using dry wood generate more total dust and a larger quantity of inhalable dust particles than do those using moist wood (IARC 1995).

Use

Wood dust is produced in woodworking industries as a by-product of the manufacture of wood products; it is not usually produced for specific uses. One commercial use for wood dust is in wood composts (Weber *et al.* 1993). "Industrial roundwood" refers to categories of wood not used for fuel, which include sawn wood (54%), pulpwood (21%), poles and pit props (14%), and wood used for other purposes, such as particle board and fiberboard (11%) (IARC 1995).

Production

Wood dust is created when machines or tools are used to cut or shape wood materials. Industries in which large amounts of wood dust are produced include sawmills, dimension mills, furniture industries, cabinetmaking, and carpentry (IARC 1995). In 1990, total estimated production of wood used in U.S. industry was 311.9 million cubic meters of softwood and 115 million cubic meters of hardwood (Demers *et al.* 1997).

Exposure

Exposure to wood dust occurs when individuals use machinery or tools to cut or shape wood. When the dust is inhaled, it is deposited in the nose, throat, and other airways. The amount of dust deposited within the airways depends on the size, shape, and density of the dust particles and the strength (turbulence and velocity) of the airflow. Particles with a diameter larger than 5 μm (inspirable particles) are deposited almost completely in the nose, whereas particles 0.5 to 5 μm in diameter (respirable particles) are deposited in the lower airways (IARC 1981, 1995).

Wood dust usually is measured as the concentration of airborne dust, by particle size distribution, by type of wood, and by other characteristics of wood. Total airborne dust concentration is reported as mass per unit volume (usually milligrams of dust per cubic meter of air). Wood dust generally is collected by a standard gravimetric method, whereby a sampling pump is used to collect a known volume of air through a special membrane filter contained in a plastic cassette. Some sampling studies reported that the particle size distribution varied according to the woodworking operation, with sanding producing smaller particles than sawing, but others found no consistent differences (IARC 1995). The majority of the wood-dust mass was reported to be contributed by particles larger than 10 μm in aerodynamic diameter; however, between 61% and 65% of the particles by count measured between 1 and 5 μm in diameter (IARC 1995).

Exposure to wood dust also occurs through handling of compost containing wood dust. One study measured dust concentrations resulting from handling of compost material consisting of successive layers of chopped leaves, bark, and wood; visible clouds of fine particles were easily generated when the compost material was agitated. The reported background concentration of respirable dust sampled upwind of the compost pile was 0.32 mg/m^3 . During loading and unloading of compost, samplers in the breathing zone detected inspirable dust at 0.74 mg/m^3 and respirable dust at 0.42 mg/m^3 . Samples collected directly from the visible clouds of particles generated by compost agitation contained inspirable dust at 149 mg/m^3 and respirable dust at 83 mg/m^3 (Weber *et al.* 1993).

The National Occupational Exposure Survey (conducted from 1981 to 1983) estimated that nearly 600,000 workers were exposed to woods (NIOSH 1990). Teschke *et al.* (1999) analyzed 1,632 measurements of personal time-weighted-average airborne wood-dust concentrations in 609 establishments on 634 inspection visits that were reported to the Occupational Safety and Health Administration Integrated Management Information System between 1979 and 1997. Exposures ranged from less than 0.03 to 604 mg/m^3 , with an arithmetic mean of 7.93 mg/m^3 and a geometric mean of 1.86 mg/m^3 . Exposure levels decreased significantly over time; the unadjusted geometric mean was 4.59 mg/m^3 in 1979 and 0.14 mg/m^3 in 1997. Occupations with high exposure to wood dust included sander in the transportation equipment industry (unadjusted geometric mean = 17.5 mg/m^3), press operator in the wood products industry (12.3 mg/m^3), lathe operator in the furniture industry (7.46 mg/m^3), and sander in the wood cabinet industry (5.83 mg/m^3). High exposures occurred in the chemical, petroleum, rubber, and plastics products industries, in sanding, pattern making, and mill and saw operations. The lowest exposures occurred in industrial pattern-making facilities, paper and paperboard mills, schools and institutional training facilities, and veneer and plywood mills.

Use of hand-held electric sanders has been identified as a particularly dusty process that leads to dust exposure. Wood-dust concentrations vary with type of dust extraction, amount of wood removed, and type of sander (Thorpe and Brown 1994). For electric belt sanders used to sand dowels, total dust concentrations ranged from 0.22 mg/m^3

with external dust extraction to 3.74 mg/m³ without extraction, and concentrations of respirable dust ranged from 0.003 mg/m³ with extraction to 0.936 mg/m³ without extraction. Rotary sanders tested with flat wood samples produced total dust concentrations ranging from 0.002 mg/m³ with extraction to 0.699 mg/m³ without extraction; concentrations of respirable dust ranged from 0.001 mg/m³ with extraction to 0.088 mg/m³ without extraction. Comparable decreases in dust concentration were observed when dust extraction was used with electrical orbital sanders.

Regulations

Occupational Safety and Health Administration (OSHA)

While this section accurately identifies OSHA's legally enforceable PELs for this substance in 2010, specific PELs may not reflect the more current studies and may not adequately protect workers. Permissible exposure limit (PEL) = 15 mg/m³ (total); 5 mg/m³ (respirable).

Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – time-weighted average (TLV-TWA) = 0.5 mg/m³ for western red cedar;
= 1 mg/m³ for all other species.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 1 mg/m³.
Listed as a potential occupational carcinogen.

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Glossary

A

- acaricide** a pesticide that kills mites and ticks
- acinar** pertaining to the smallest division of a gland; a group of secretory cells surrounding a cavity
- acute** the clinical term is used for a disease having a short and relatively severe course; in rodent testing, usually pertains to administration of an agent in a single dose
- acute lymphocytic leukemia** (also called acute lymphoblastic leukemia, acute lymphoid leukemia, acute lymphatic leukemia) a group of neoplasms composed of immature precursor B or T lymphocytes (lymphoblasts)
- acute myeloid leukemia** (also called acute myelogenous leukemia or acute nonlymphocytic leukemia) a group of neoplasms composed of immature precursor cells of the bone marrow which are not of the lymphocyte lineage, i.e., erythrocyte, granulocyte, monocyte, and platelet lineages
- adduct** a complex that forms when a chemical binds to a biological molecule such as DNA or a protein
- adenocarcinoma** a malignant neoplasm of epithelial cells with a gland-like appearance
- adenoma** a benign neoplasm of epithelial tissue in which the neoplastic cells form glands or gland-like structures in the stroma
- adenomatous** pertaining to adenoma or to nodular hyperplasia of a gland
- adenomatous polyp** benign neoplastic tissue originating in glandular epithelium
- adipose tissue** fatty tissue
- adjuvant therapy** therapy involving both a primary therapy and an additional treatment that enhances the action of the primary therapy
- adrenal gland** a hormone-secreting organ located above each kidney
- aerodynamic diameter** a physical property of a particle or fiber in a viscous fluid such as air that takes into account the geometric dimensions of the substance and its density
- aerosol** a dispersed suspension of fine particles in gas
- albino** an organism exhibiting deficient pigmentation in skin, eyes, and hair
- alkaline** basic (as opposed to acidic); a material whose index of acidity (pH) is above 7
- alkyd** any of several synthetic resins made by heating together a polybasic acid, such as phthalic or maleic acid, and a polyhydric alcohol, such as glycerin or a glycol; these resins are used in paints, varnishes, and lacquers
- alkylating agent** a substance that causes the incorporation of single-bonded carbon atoms into another molecule
- allele** any one of a series of two or more different genes that occupy the same position (locus) on a chromosome
- alveolar/bronchiolar** pertaining to the alveoli or bronchi of the lungs
- alveoli** usually referring to small, sac-like pouches in the portion of the lungs where gas exchange with the blood occurs; also, sac-like structures in certain glands or in the jaws where the teeth arise
- alveolitis** inflammation of the alveoli or an alveolus
- ambient air** outdoor air to which the general public is exposed
- ameloblastoma** a malignant jaw tumor which stems from the ameloblasts, cells which form tooth enamel
- amenorrhea** the absence or abnormal cessation of menstruation
- amine** an organic compound that may be derived from ammonia (NH_3) by the replacement of one or more hydrogen atoms (H) by hydrocarbon groups or other chemical moieties; replacing one, two, or three hydrogen atoms gives primary, secondary, or tertiary amines, respectively, and if a fourth group is added to a tertiary amine (R_3N), the compound formed is called a quaternary amine (R_4N^+) and the nitrogen carries a positive charge
- amyloidosis** the accumulation of amyloid, an abnormal complex material composed of protein and carbohydrate, in body tissues
- anabolic steroid** a synthetic derivative of testosterone, a male sex hormone; used principally to promote growth and repair of body tissues in senility, debilitating illness, and convalescence
- analgesic** a pain-relieving agent that does not cause loss of consciousness
- analogue** 1. one of two organs or parts in different species of animals or plants that differ in structure or development but are similar in function 2. a compound that resembles another in structure; may be an isomer, but not necessarily
- analytical grade** the highest available purity of a chemical
- anaplastic** a term used to describe cancer cells that divide rapidly and have little or no resemblance to normal cells
- androgen** a steroid hormone that is responsible for masculine characteristics
- anemia** lower than normal limits of circulating red blood cells
- anesthetic** a substance used to prevent the sensation of pain
- aneuploidy** abnormal number of chromosomes
- angiosarcoma** a type of malignant neoplasm of a blood vessel
- anion** an ion that carries a negative charge, e.g., chloride (Cl^-), sulfate (SO_4^{2-}), and acetate (CH_3CO_2^-); anions form salts with cations other than H^+ , while the corresponding acids are formed when combined with H^+ ions
- anthropogenic** caused by humans
- antibiotic** a chemical substance, produced by or derived from an organism, which is capable of killing or inhibiting the growth of other organisms
- anticonvulsant** a substance that lessens the severity of convulsions
- antiepileptic** a substance that lessens the severity of epileptic seizures
- anthelmintic** (also called anthelmintic) a drug used to treat parasitic infestations caused by helminths (parasitic worms)
- anti-inflammatory** counteracting or suppressing inflammation, which is characterized by heat, redness, edema, and pain in the involved part of the body
- antimicrobial** a substance that kills microorganisms or arrests their multiplication or growth or otherwise prevents their pathogenic action; microbes include bacteria, fungi, and protozoa
- antineoplastic** inhibiting the survival and proliferation of malignant and benign neoplastic tumors
- antioxidant** a substance that inhibits chemical oxidation of another material
- antiseptic** a substance that inhibits the growth of microorganisms on living tissue
- aplastic anemia** a severe form of anemia that is characterized by decreased maturation of stem cells
- apoptosis** a mechanism of cellular suicide that requires energy to occur; also called programmed cell death
- aquaculture** the production of food by growing plants or animals in water
- aqueous** relating to, similar to, containing, or dissolved in water
- aquifer** geologic formation containing sufficient saturated porous and permeable material to transmit water

aromatic hydrocarbon an organic chemical compound formed primarily from carbon and hydrogen atoms with a structure based on benzene rings; substituents on the rings(s) may contain atoms other than carbon or hydrogen

arsenical a compound containing arsenic

arterial relating to one or more arteries or to the entire system of arteries

arteritis inflammation of an artery

ascaricide an agent destructive of round- or thread-worms which occur as intestinal parasites

aspect ratio the ratio of a fiber's length to its diameter

assay procedure whereby a property or concentration of an analyte is measured; a scientific test

astrocytoma a tumor composed of astrocytes (glial cells with fibrous protoplasmic processes); the most common type of primary brain tumor and also found throughout the central nervous system

auditory sebaceous gland a gland that secretes an oily substance and that is located in the inner layer of the ear's skin

autoignition temperature the minimum temperature required to cause self-sustained combustion without any other source of heat

autoimmune disease (also called autoimmune disorder) a condition in which one's own body or its components are subject to deleterious effects of its immune system

autoimmune hemolytic anemia anemia that occurs in some autoimmune diseases

azide a compound that contains the monovalent $-N_3$ group

azo- a prefix denoting the presence in a molecule of the group $-N=N-$ (see also diazo-)

B

bactericide an agent (e.g., heat, light, or osmotic pressure) or a chemical that kills bacteria or inhibits their growth

bacteriophage a virus with specific affinity for bacteria

bacteriostat an agent that inhibits the growth or multiplication of bacteria

bacteriostatic inhibiting the growth or multiplication of bacteria

basal-cell carcinoma an epithelial tumor of the skin that seldom metastasizes but has the potential for local invasion and destruction; it usually occurs as one or several small pearly nodules with central depressions on the sun-exposed skin of older adults

batt precut panels of insulation available in a variety of widths, lengths, and thermal resistance ratings (i.e., R-values)

benign tumor an abnormal mass of tissue that does not spread beyond normal tissue boundaries

betel quid an addictive mix of betel leaf, areca nut, and slaked lime that is chewed in some Pacific and Asian cultures; its use is associated with aggressive oral cancers affecting especially the inner lining of the cheeks and lips, but also affecting the tongue, lower lip, tonsil and floor of the mouth

bile a fluid produced in the liver and stored in the gallbladder that emulsifies fats and other hydrophobic compounds aiding in their absorption or excretion through the intestine

bile duct a tube through which bile passes from the liver or gallbladder to the small intestine, composed of the following three segments: common hepatic duct, cystic duct, and common bile duct

bilirubin a pigment produced by the breakdown of heme from red blood cells

bioaccumulation the process by which a material in an organism's environment progressively accumulates within the organism

bioassay the determination of the potency or concentration of a compound by its effect upon animals, isolated tissues, or microorganisms, as compared with a chemical or physical assay

bioavailability the extent to which an organism will absorb a chemical into its blood

bioconcentrate accumulation of a chemical in tissues of a fish or other organism to levels greater than in the surrounding medium

biodegradation the decomposition of a material by microorganisms; the conversion within an organism of molecules from one form to another, a change often associated with change in pharmacologic activity

biodurability the rate of removal of a substance, such as a fiber, from the lungs by dissolution or disintegration

biopersistence the ability of a substance, such as a fiber, to remain in the lung; biopersistence is a function of the material's solubility and the biological ability of the lung to clear the fiber

biotransformation the conversion within an organism of molecules from one form to another; a change often associated with change in pharmacologic activity

blackfoot disease a disease seen in Taiwan that is caused by exposure to arsenic via drinking water; severe damage to the blood vessels of the lower limbs leads to gangrene

boiling point the temperature of a liquid at which the vapor pressure of the liquid equals environmental pressure surrounding the liquid

bowel the intestine, or the part of the digestive tract extending from the stomach to the anus

breakdown product a chemical derived from a parent compound that has been altered, usually by heat, light, or enzymes

bronchiogenic carcinoma a carcinoma originating in the bronchi of the lung

bronchiole a small division of a bronchus (lung airway)

bronchioloalveolar derived from epithelium of terminal bronchioles

bronchoalveolar (also called bronchovesicular) relating to the bronchial tubes and alveoli in the lungs

bronchoalveolar lavage a technique used to obtain a sample of the cells, fluids, and other materials present in the very small airways and alveoli of the lung by instilling saline into the airway via a bronchoscope

bronchogenic originating in one of the larger air passages in the lung

buccal cavity the vestibule in the mouth between the teeth and the cheeks

buffer a mixture of an acid and its conjugate base that, when present in a solution, reduces any changes in pH that would otherwise occur in the solution when acid or alkali is added to it

C

calendarizing a process of smoothing or glazing paper or cloth by pressing it between plates or passing it through rollers

cancer a general term used to indicate any of various types of malignant neoplasms

carbonization the process of converting an organic compound to carbon or to a carbonic residue

carcinogen any cancer-producing substance

carcinogenesis the process by which normal tissue becomes cancerous

carcinogenicity the power, ability, or tendency to produce cancerous tissue from normal tissue

carcinoma a malignant neoplasm of epithelium

cardiovascular of, relating to, or involving the heart and blood vessels

carina a projection of the lowest tracheal cartilage at the bifurcation of the airway into the right and left primary bronchi

case-control study an investigation in which select cases with a specific diagnosis are compared to individuals from the same or related population(s) without the diagnosis

catalyze to increase the rate of a chemical reaction using material that usually remains unchanged at the end of the reaction

cation an ion carrying a positive electrical charge

causalgia a complex regional pain syndrome characterized by burning pain and marked sensitivity to touch in the distribution of an injured peripheral nerve

C-cell a cell type of the thyroid gland, with numerous small secretory granules and a light colored cytoplasm; they also are the source of calcitonin and are also called clear cells

cecum sac-like part of the large intestine between the small intestine and the colon

ceiling limit maximum allowable human exposure concentration of an airborne substance that should not be exceeded, even for an instant

central nervous system the part of the nervous system consisting of the brain and spinal cord

centromere the point of attachment of the two chromatids of a chromosome

cerebral ependymoma a neoplasm that forms from the cells lining the spinal cord's central canal or the ventricles of the brain

cervix a neck-like structure or constriction; most often used to refer to the neck of the uterus

cetane number a measure of ignition quality of diesel fuel; the higher the cetane number the easier the fuel ignites when injected into an engine (the cetane number is the diesel equivalent to octane)

chelating agent a substance used to reduce the concentration of free metal ion in solution by complexing it; often used to remove toxic metals from the body

chelation a complex formation involving a metal ion and two or more polar groupings of a single molecule; chelation can be used to remove an ion from participation in biological reactions, as in the chelation of Ca^{2+} in blood by EDTA

chemical intermediate a chemical formed or used during the process of producing another chemical

chemosterilant 1. a chemical compound that causes an organism to become sterile after exposure to it 2. a chemical that kills microorganisms

chemotherapy the treatment of disease with chemical agents

chirality the property of nonidentity of an object with its mirror image; used in chemistry with respect to stereochemical isomers

cholangiocarcinoma a malignant bile-duct neoplasm

cholangiocellular of or pertaining to the gallbladder or bile duct

cholesteatoma a cyst lined by stratified squamous epithelium, which is filled with desquamating debris and cholesterol; also called pearl tumor

choroidal melanoma a neoplasm in the choroid (a layer of vascular tissue enveloping most of the eye that arises from melanocytes)

chromatid each of the two strands formed by the duplication of a chromosome during mitosis or meiosis

chromatin the genetic material of the nucleus, consisting of DNA and nuclear proteins found in chromosomes

chromophobe adenoma an adenoma of the chromophobe cells of the anterior pituitary gland that is hormonally inactive

chromosomal aberrations any abnormality of a chromosome's number or structure

chronic continuing for a long period of time; in rodent testing, pertains to dosing schedules longer than 3 months

chronic lymphocytic leukemia a slowly progressing lymphoid leukemia arising usually from B cells, but occasionally from T cells or NK cells

chronic myelogenous leukemia a group of slowly progressing neoplasms composed of immature precursor cells of the bone marrow which are not of the lymphocyte lineage, i.e., erythrocyte, granulocyte, monocyte, and platelet lineages

circulatory system the cardiovascular and lymphatic systems make up the circulatory system involved in circulating blood and lymph throughout the body; the cardiovascular system consists of blood, blood vessels, and the heart, while the lymphatic system consist of lymph, lymphatic vessels, and lymph nodes

cirrhosis replacement of normal liver tissue with bands of fibrous tissue surrounding nodules of regenerating liver tissue; characterized by inflammation, pain, and jaundice or icterus (i.e., yellow discoloration of the skin)

Clara cells unciliated cells found in the epithelium of the respiratory and terminal bronchioles which secrete some components of pulmonary surfactant

clastogen an agent capable of causing breakage of chromosomes

clear-cell adenocarcinoma a rare tumor, usually of the female genital tract, which looks clear when viewed under a microscope

clitoral gland (also called preputial gland of the clitoris) sebaceous glands of the female prepuce (folds of skin covering the clitoris equivalent to the foreskin of the penis); the male equivalent is called preputial gland or Tyson's gland

co-carcinogen an agent that is not carcinogenic itself, but enhances the activity of another agent that is carcinogenic

codon a sequence of three nucleotides in a strand of DNA or RNA that provides genetic code information for a specific amino acid

cohort studies a study of a group of people matched against a second group similar to it except for one factor (usually the suspected cause of a disease)

colitis inflammation of the colon

colon the part of the large intestine extending from the cecum to the rectum

colorectal relating to the colon and rectum, or to the entire large intestine

commercial grade less than the purest available form of a chemical; the purity normally produced for and adequate for commercial uses

confounding a relationship between the effects of two or more causal factors observed in a set of data such that it is not logically possible to separate the contribution of any single causal factor to the observed effects

congener one of two or more things that are similar or closely related in structure, function, or origin

congenital existing from birth

conjugated bound together; in organic chemistry, conjugated refers to a molecular structure or substructure containing alternating double and single bonds between pairs of adjacent atoms

conjunctiva the membrane that lines the eyelid and covers part of the eyeball

connective tissue a tissue that connects, supports, or surrounds other tissues or organs

contaminant an impurity; in the environment, a chemical that is not ordinarily present and that may have deleterious effects

copolymers a polymer of two or more different monomers

cortical having to do with the cortex, the outer portion of an organ

corticosteroids adrenal cortex hormones

covalent binding a bond in which each atom of a bound pair contributes one electron to form a pair of electrons

creatinine a waste product of muscle metabolism that is found in blood and urine; blood and urinary levels can be used to measure creatinine clearance to determine kidney function

cross-linking the extension of chemical bonds in more than one direction (not just linearly); serves to strengthen polymers

cystadenocarcinoma a malignant glandular neoplasm that forms cysts

cystadenoma a benign glandular neoplasm that forms cysts

cytochrome a class of hemoproteins whose principal biological function is electron and/or hydrogen transport

cytogenetic the cellular constituents concerned in heredity

cytotoxic an agent that is toxic to cells

D

D- (or **L-**) used separately, prefixes of **D-** for dextrorotary (rotated to the right) or **L-** for levorotary (rotated to the left) before the same chemical name refer to designations for optically active isomers that are chemically identical but that rotate plane polarized light in opposite directions, the isomers are mirror images of each other; when used together, **DL-** designates a racemic mixture of the two isomers whose optical activities cancel each other

dam female parent

defoliant a chemical spray or dust that causes leaves to drop off plants prematurely

dehydrogenation the removal of one or more hydrogen ions or protons from a molecule

deliquescent tending to melt or dissolve; especially tending to undergo gradual dissolution and liquefaction by the attraction and absorption of moisture from the air

density amount of mass per unit volume; the density for solids and liquids is typically expressed in grams per cubic centimeter (g/cm^3) and is generally assumed to refer to temperatures near room temperature unless otherwise stated, while the values for gases generally are the calculated ideal gas densities in grams per liter at 25°C and 101.325 kPa

dermatitis an inflammation of the skin

dermatomyositis an inflammation of the skin, subcutaneous tissue, and muscles, involving death of muscle fibers

dermis the sensitive inner layer of the skin

diabetes a disease in which the body's ability to use sugar is impaired and which usually involves the abnormal appearance of sugar in the urine

diamine an organic compound containing two amine groups, e.g., ethylenediamine, $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$

diazo- a prefix denoting a compound containing the $-\text{N}'\text{N}'-$ or $-\text{N}=\text{N}^+$ group (see also azo-)

differentiated cells cells which have lost or have a limited capacity to transform into other cell types which have functions different from the cell it originated from (pluripotency); this is the opposite of stem cells which have the ability to transform into other cell types, though there are multiple cell types between the two extremes which have different capacities of pluripotency

diffusion coefficient the rate at which a substance moves from an area of high concentration to an area of low concentration

dimer a compound or unit produced by the combination of two like molecules

dissociation constant ($\text{p}K_a$) the equilibrium constant for the breaking apart of a weak acid into its hydrogen and conjugate base in a water solution

dissolution the act or process of dissolving

distant tumor a tumor located far from the point at which abnormal growth originated

distillation the separation or purification of the components of a material by gradually increased heating and removal of the components that vaporize at different boiling points

DL- designates a racemic mixture of two isomers whose optical activities cancel each other

dorsal relating to the back or posterior of an organ or organism

dose-response relationship a relationship between several doses or concentrations of a chemical, biological, or physical agent to which an organism is exposed and the degree of the monitored effect

duodenum the first division of the small intestine, which is about 25 cm in length

dysfunctional uterine bleeding abnormal bleeding of the uterus

dysplasia abnormal tissue growth or development

E

eczema an inflammation of the outer layer of skin, characterized by redness, itching, crusting, and scaling

edema an accumulation of an excessive amount of watery fluid in cells, tissues, or serous cavities

effluent wastewater discharged from a treatment plant, sewer, or industrial outfall into the environment, usually to surface waters

electrolyte a substance, such as sodium chloride (NaCl), that dissociates into ions when fused (melted) or in solution, thereby becoming capable of conducting an electric current

electrophile the electron-attracting atom or agent in an organic reaction

electrophilic relating to an electrophile

emulsifier an agent that causes the dispersion of one insoluble fluid into another fluid

enantiomer one of a pair of compounds having a mirror image relationship (stereoisomers)

endogenous originating within an organism

endogenously derived or produced internally

endometrium the mucous membrane lining of the uterus

end use the final intended purpose for a chemical or an item

Entamoeba histolytica a microorganism that causes disease, particularly of the digestive tract

environmental fate the distribution and transformation of a chemical from its first release until its ultimate removal from or recycling through the environment

enzyme a protein produced in organisms capable of accelerating a particular biochemical reaction; a biological catalyst

eosinophil a granular leukocyte with a nucleus that usually has two lobes connected by a slender thread of chromatin and is readily stained by eosin

epidemiology science concerned with the occurrence and distribution of disease in populations

epidermis the outer layer of skin

epidermoid tumor (also called epidermoid carcinoma) another name for squamous cell carcinoma

epididymis a coiled segment of the spermatic ducts that serves to store and transport spermatozoa between the testis and the vas deferens

epigenetics changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence

epilepsy a neurological disease usually characterized by seizures involving convulsions and loss of consciousness

epithelial relating to or consisting of epithelium

epithelium tissue that lines the surface and cavities and is a part of glandular structures in the body

erythema redness of the skin produced by congestion of the capillaries

erythrocytes cells that carry oxygen to all parts of the body (red blood cells)

esophagus the passage through which food travels from the throat to the stomach

esthesioneuroepithelioma a tumor consisting of undifferentiated cells of sensory nerve epithelium

esthesioneuroma (also called olfactory neuroma) a nasal cavity tumor of nervous tissue from olfactory epithelium

estrogen any of a group of female sex hormones

estrogen-sensitive tissues those tissues affected by the presence of estrogens

estrus the recurrent, restricted period of sexual receptivity in female mammals, other than humans, marked by intense sexual urge

eukaryote an organism whose cells contain a limiting membrane around the nuclear material and which undergoes mitosis

eukaryotic pertaining to a eukaryote

Ewing's sarcoma a malignant tumor of the bone, accompanied by pain and fever

exogenous developed or originating outside the body

extrahepatic outside of or unrelated to the liver

exposure-response relationship a relationship between several doses or concentrations of a chemical, biological, or physical agent to which an organism is exposed and the degree of the monitored effect

F

Fanconi anemia (also called Fanconi's anemia) a congenital disorder affecting all bone marrow elements, resulting in anemia, leucopenia, and thrombopenia, and is associated with cardiac, renal, and limb malformations as well as dermal pigmentary changes; spontaneous chromosome breakage is a feature of this disease along with predisposition to leukemia

feedstock the raw material supplied to a processing plant that eventually create an end product

Fenton reaction the iron(II)-salt-dependent decomposition of hydrogen peroxide generating a highly reactive hydroxyl radical

ferruginous body a mineral particle to which pulmonary macrophages have added an iron protein coat; ferruginous bodies are used as an indicator of exposure to specific dusts or fibers

fiber a particle with a length to width ratio of at least 3:1

fibroadenoma a benign neoplasm formed of glandular and connective tissue

fibroblasts the most common connective tissue cell type

fibroma a benign neoplasm derived from fibrous connective tissue

fibrosarcoma a type of soft tissue sarcoma that begins in fibrous tissue that holds bones, muscles, and other organs in place

flammable that which will burn readily or continuously

flash point the lowest temperature at which enough vapor of a combustible liquid forms to ignite momentarily in air

flocculation precipitation from solution in the form of fleecy masses; the process of becoming flocculent

flux the rate of mass flow across a unit area

follicular cell a modified epithelial cell that secretes fluid

forestomach a non-glandular expansion of the alimentary canal between the esophagus and the glandular stomach; rodents have a forestomach and a glandular stomach, whereas, humans have only a glandular stomach

formalin a solution of formaldehyde in water typically containing 37% formaldehyde by mass and 10% to 15% methanol as a stabilizer

fumigant a pesticide in vapor or gaseous form used to kill pests or disinfect materials

fungicide a pesticide used to control, prevent, or kill fungi

fungus a lower plant that feeds on other organic matter and lacks the chlorophyll and tissue differentiation of higher plants

G

gallbladder a reservoir for bile located near the liver

gastrointestinal tract the part of the digestive system composed of the stomach and intestine

gavage in animal experiments, the introduction of material through a tube passed through the mouth into the stomach; also called gastric, stomach, or oral intubation

gene a unit of hereditary information; the portion of a DNA molecule that contains, coded in its nucleotide sequence, the information required to determine the amino acid sequence of a single polypeptide chain

genitourinary pertaining to the genital and urinary organs

genotoxicity the amount of damage caused to a DNA molecule

genotype genetic constitution of an individual

germ cells cells which give rise to the male and female gametes (the sperm and ova)

gestation pregnancy; in mammals, the period during which the young develops between the egg's fertilization and birth

Giardia lamblia a microorganism causing gastrointestinal infection in humans and other mammalian hosts

gland an aggregation of cells, specialized to secrete or excrete certain biologically important materials

glandular stomach the muscular sac between the esophagus and the small intestine containing glandular tissue; the glands of the stomach secrete mucous, hydrochloric acid, and digestive enzymes

glass fiber general term that may be used to refer to reinforcing glass filament, glass wool, or superfine glass fiber

glass wool a fibrous product formed by blowing or spinning molten glass; the resultant fibers are collected as a tangled mat of fibrous product

glioma any neoplasm derived from one of the various types of cells that form the interstitial tissue of the brain, spinal cord, and retina; e.g., astroblastoma, astrocytoma, glioblastoma multiforme, ganglioglioma, spongioblastoma polare, medulloblastoma, ependymoma, oligodendroglioma, etc.

glomeruli a small intertwined group of capillaries within nephrons of the kidney that filter the blood to make urine

glomerulonephritis a disease characterized by inflammation of the glomeruli

grand mal epilepsy an extreme form of epilepsy, with seizures involving loss of consciousness and generalized convulsions

granulocyte a mature granular leukocyte; classified as either neutrophils, basophils, or eosinophils

granulosa cell a cell lining the vesicular ovarian follicle that becomes a luteal cell after ovulation

gray cast iron a cast iron alloy with a graphitic microstructure

H

half-life the time required for a substance to be reduced to one-half its present value through degradation or through elimination from an organism

hamartoma a focal malformation that resembles a neoplasm, grossly and even microscopically, but results from faulty development in an organ; it is composed of an abnormal mixture of tissue elements, or an abnormal proportion of a single element, normally present in that site, which develop and grow at virtually the same rate as normal components, and are not likely to result in compression of adjacent tissue (in contrast to neoplastic tissue)

Harderian glands in some animals, accessory tear glands excreting a fluid that facilitates movement of the third eyelid, an extra fold of skin in the eye

hard palate the bony front portion of the partition separating the mouth from the nasal cavity

healthy-worker effect phenomenon of workers usually exhibiting overall death rates lower than those of the general population due to the fact that the severely ill and disabled are ordinarily excluded from employment

hemangioendothelioma (also called hemangiosarcoma) a malignant tumor characterized by rapidly proliferating cells derived from the blood vessels and lining irregular blood-filled spaces

hemangioendotheliosarcoma a hemangiosarcoma formed by proliferation of endothelial tissue

hemangioma a benign tumor made up of newly-formed blood vessels

hemangiosarcoma (also called hemangioendothelioma) a malignant tumor characterized by rapidly proliferating cells derived from the blood vessels and lining irregular blood-filled spaces

hematinic acting to improve the quality of blood, as by increasing hemoglobin concentration or stimulating red blood cell formation

hematocrit the volume percentage of the erythrocytes in the whole blood

hematopoietic pertaining to the formation of blood or blood cells

heme the prosthetic, oxygen-carrying, color-furnishing constituent of hemoglobin

hemoglobin the red, respiratory protein of erythrocytes; transports oxygen from the lungs to the tissues

hemolymphoreticular pertaining to the network of cells and tissues of the blood and lymph nodes found throughout the body

Henry's law the relationship that defines the partition of a soluble or partially soluble species between the gas and solution phases

Henry's law constant the ratio of the aqueous-phase concentration of a chemical to its equilibrium partial pressure in the gas phase; the larger the Henry's law constant the less soluble it is (greater tendency for vapor phase)

hepatectomy removal of the liver

hepatic pertaining to the liver

hepatitis an inflammation of the liver

hepatoblastoma a malignant neoplasm occurring in young children, primarily in the liver, composed of tissue resembling embryonal or fetal hepatic epithelium, or mixed epithelial and mesenchymal tissues

hepatocellular pertaining to cells of the liver

hepatocellular carcinoma malignant liver-cell neoplasm

hepatocyte a parenchymal liver cell

hepatotoxic a substance that is toxic to the liver

herbicide an agent that is destructive to plants

histology the branch of anatomy that deals with microscopic structure, composition, and function of tissues

histones the chief protein components of chromatin; they act as spools around which DNA is wound and play a role in gene regulation

Hodgkin's disease (also called Hodgkin's lymphoma) a form of malignant lymphoma characterized by painless progressive enlargement of the lymph nodes, spleen, and general lymphoid tissue

hormone any of various chemical substances that are produced by the endocrine glands and that have specific regulatory effects on the activity of certain organs

hydrolysis a chemical reaction in which the interaction of a compound with water results in the decomposition of that compound

hydrolyze to subject to hydrolysis

hydroxyl the atom group or radical OH

hydroxylation the placing of a hydroxyl group on a compound in a position where one did not exist before

hydroxyl radicals very reactive free radicals that can damage cellular macromolecules; formed when superoxide radicals react with hydrogen peroxide

hyperplasia the abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue

hyperthyroidism excessive activity of the thyroid gland and the resultant pathological condition characterized by increased metabolism, enlargement of the thyroid gland, rapid heart rate, and high blood pressure

hypertrophy increase in volume of a tissue or organ produced entirely by enlargement of existing cells

hypnotic sleep-inducing; a drug that induces sleep

hypogonadism (also called hypogonitalism) a condition resulting from or characterized by abnormally decreased functional activity of the gonads, with retardation of growth and sexual development

I

ileum the third portion of the small intestine, about 12 feet long, extending from the junction with the jejunum to the ileocecal opening

immunosuppression artificial prevention or diminution of the natural immune response (e.g., by irradiation or by administration of substances such as pharmaceutical antimetabolites or specific antibodies to prevent sensitization); immunosuppression or immunodeficiency may also be used to describe the condition of acquired or congenitally lowered immune response

implantation the insertion of a mass of material into an organism at a fixed site from which the mass does not move except by dissolving in the body fluids

incidence rate at which new cases occur

inhalation the drawing of air or other substances into the lungs

initiator a chemical that permanently alters a cell or group of cells and, in the case of carcinogens, can cause tumors if the cells divide

injection site the site, usually in the skin, at which an agent is injected into an organism; this site may exhibit effects resulting from exposure to the agent combined with tissue injury from the injection syringe

inorganic pertaining to materials or chemicals that do not contain carbon (for instance, glass or table salt)

in situ Latin phrase meaning confined to the site of origin; a cancer that has not metastasized or invaded neighboring tissues

insoluble incapable of being dissolved in a particular solvent

insulinoma a tumor of the beta islet cells of the pancreas, which is usually benign and secretes insulin and may cause low blood glucose levels, hypoglycemia

International Organization for Standardization (ISO) a non-governmental organization made up of representatives from national standards bodies that serves as an international standard-setting body

interstitial relating to or situated in the small, narrow spaces between tissues or parts of an organ

intra-abdominal within the abdomen (the portion of the body between the thorax (chest cavity) and the pelvis)

intra-bronchial situated or occurring within a bronchus (a division of the respiratory tract below the trachea (windpipe) that leads into the lung)

intra-gastric within the stomach

intra-medullary within the spinal cord, the medulla oblongata of the brain, or the bone marrow

intramuscular injection an injection into muscle tissue

intra-peritoneal injection injection within the peritoneal cavity, i.e., the area that contains the abdominal organs

intrapleural within the pleura, a membrane that secretes fluid, envelops the lungs, and lines the walls of the cavity containing them

intrapleural injection injection within the pleura, a membrane that secretes fluid, envelops the lungs, and lines the walls of the cavity containing them

intrathoracic implantation implantation within the thoracic cavity, i.e., the area that contains the heart and lungs

intratracheal within the trachea (windpipe)

intratracheal instillation instillation within the trachea

intravenous injection an injection into a vein

intravesicular within membranes or fluid-filled pouches (such as the urinary bladder or the alveoli)

in utero Latin phrase meaning within the uterus

invasive spreading beyond specific body tissues

Inventory Update Rule (IUR) the Toxic Substances Control Act (TSCA) Section 8(a) authorizes the U.S. EPA to collect certain information on chemical substances manufactured or processed in the United States, and the IUR is a periodic collection of information on the chemical substances currently in commerce; through the IUR, the Agency obtains a periodic collection of information on more than 83,000 chemical substances listed on the TSCA Inventory

in vitro Latin phrase meaning biological process taking place in a test tube, culture dish, or elsewhere outside a living organism

in vivo Latin phrase meaning biological processes taking place in a living organism

iron-deficiency anemia anemia that is characterized by low or non-existent iron stores and low concentrations of iron in the blood and that has such symptoms as pallor, mouth sores, digestive difficulties, and thin, brittle nails

islet-cell cell of the islets of Langerhans (the endocrine portion of the pancreas that is composed of alpha cells which secrete glucagons, beta cells which secrete insulin, and delta cells which secrete somatostatin)

isomer one of two or more variations of a chemical, each of which has the same chemical formula but a different structural arrangement

isozyme any of the chemically distinct forms of an enzyme that perform the same biochemical function

J

jaundice a yellowish staining of the integument (skin), sclerae (whites of the eyes), and deeper tissues caused by an excess of bilirubin in the blood

jejunum the portion of small intestine, about 8 feet in length, between the duodenum and ileum

K

Kaposi's sarcoma a multifocal malignant or benign neoplasm of primitive vasoformative (relating to the formation of blood or lymphatic vessels) tissue, occurring in the skin and sometimes in lymph nodes or viscera; development of this neoplasm is associated with HIV infection and especially co-infection with Kaposi's sarcoma herpesvirus (human herpesvirus type 8)

K_{dis} the dissolution rate (K) of a fiber *in vitro*; it is typically determined by elemental analysis of the flow-through solution to measure the mass of material leached from the fibers over a given time, and expressed in units of ng/cm² per hour

keratinizing squamous-cell types squamous cells with keratin in the cytoplasm

keratoacanthoma a rapidly growing skin tumor having a central keratin mass and usually occurring on exposed areas, invading the dermis but remaining localized and usually healing spontaneously

K_{ow} (octanol-water partition coefficient) a measure of the equilibrium concentration of a compound between octanol and water

L

L- (or D-) used separately, prefixes of L- for levorotary (rotated to the left) or D- for dextrorotary (rotated to the right) before the same chemical name refer to designations for optically active isomers that are chemically identical but that rotate plane polarized light in opposite directions, the isomers are mirror images of each other; when used together, DL- designates a racemic mixture of the two isomers whose optical activities cancel each other

labile refers to the ability of a particular complex ion to participate rapidly in reactions that result in replacing one or more ligands in its coordination sphere (the opposite of labile is inert); "inert" and "labile" are not to be confused with "stable" and "unstable" which refer to the thermodynamic tendency of chemical species to exist under equilibrium conditions

lactation the secretion of milk

laminating separating or arranging in layers

large intestine the lower portion of the intestine; a membranous tube extending from the small intestine to the anus; includes the cecum, colon, and rectum

laryngeal cancer cancer of the larynx

larynx also called the voice box, it is located below the pharynx in the neck

latency the time between the instant of stimulation (exposure to a substance) and the beginning of a response (disease)

leachate the liquid produced in a landfill from the decomposition of waste within the landfill

leiomyoma a benign tumor of smooth muscle, the type of muscle that is found in the heart and uterus; a leiomyoma of the uterus is commonly called a fibroid

leiomyosarcoma a malignant tumor of smooth muscle cells that can arise almost anywhere in the body, but is most common in the uterus, abdomen, or pelvis

leukemia a cancer of the blood-forming tissues that is characterized by a marked increase in the number of abnormal white blood cells (leukocytes) in the bone marrow and peripheral blood

leukocyte white blood cell; includes lymphocytes, granulocytes, monocytes

levorotatory of or relating to an optically active chemical that rotates the plane of polarized light to the left, or counterclockwise

Leydig cell a cell in the testes that secretes the hormone testosterone

ligand any molecule or ion that binds to the surface of a protein by noncovalent bonds

lipid any of various fats or waxes, which, along with proteins, carbohydrates, and nucleic acids, form the principal constituents of living cells

lipophilic having a strong affinity for fats

lipophilicity the affinity of a molecule or a moiety for a lipophilic environment

log octanol-water partition coefficient (log K_{ow}) the ratio of concentrations of a substance in octanol and in water when dissolved in a mixture of octanol and water (for convenience, the logarithm of K_{ow} is used); the octanol-water partition coefficient of a substance is useful as a means to predict soil adsorption, biological uptake, lipophilic storage, and bioconcentration

lupus erythematosus an autoimmune disease of two forms:

- (1) discoid lupus erythematosus, in which chronic inflammation is limited to the skin and is characterized by scales that leave scars, and
- (2) systemic lupus erythematosus, which affects many other organs such as the joints, kidneys, nervous system, and mucus membranes

lymph a clear liquid that is collected from the tissues throughout the body and that flows in lymphatic vessels

lymphatic pertaining to the lymph, lymph nodes, or vascular vessels that transport lymph to the lymph nodes

lymphocyte a mononuclear leukocyte that is primarily a product of lymphoid tissue and participates in humoral and cell-mediated immunity

lymphocytic leukemia a neoplasm composed of premature lymphocytes growing in the bone marrow, usually of B-cell lineage

lymphohematopoietic of, relating to, or involved in the production of lymphocytes and cells of blood, bone marrow, spleen, lymph nodes, and thymus

lymphoid resembling lymph or lymphatic tissue

lymphoma a neoplasm of the lymphatic tissue

lymphopoietic relating to the formation of lymph

lymphoreticular pertaining to reticuloendothelial cells (monocytes and resident tissue macrophages)

lymphosarcoma any of various malignant neoplastic disorders of lymphoid tissue, excluding Hodgkin's disease

M

macrophage a large cell that is present in blood, lymph, and connective tissues, removing worn out cells and cell products, harmful microorganisms, and foreign material from the bloodstream

malignant tending to become progressively worse; life-threatening

mammary pertaining to the breast or mammary glands

mastodynia a pain in the breast

mastomys a small rodent (multimammate mouse of the genus *Mastomys*) used in certain laboratory experiments

medulla the inner core of certain organs or body structures, such as the marrow of bone

megakaryocyte a large cell of the bone marrow that gives rise to platelets, the blood cells which function in blood clotting

meiosis process of cell division that results in the formation of gametes, consisting of two nuclear divisions in rapid succession that result in the formation of four gametocytes each containing half the number of chromosomes found in somatic cells

melanocyte cells of the skin that produce the pigment melanin

melanoma a neoplasm derived from cells that are capable of forming the pigment melanin

melanotic schwannoma a neoplasm of a Schwann cell (a cell that wraps around the axon of peripheral nerves forming a myelin sheath) that contains granules of melanin, melanosomes, and is usually benign

melting point 1. the melting point of the substance at atmospheric pressure (101.3 kPa); 2. when there is a significant difference between the melting point and the freezing point, a range is given; 3. in the case of hydrated substances (i.e., those with crystal water), the apparent melting point is given; 4. if the substance decomposes at or below its melting point, this is noted (dec)

meningioma a slow-growing tumor of the meninges, often creating pressure and damaging the brain and adjacent tissues; occurs most often in adults

menopause the cessation of menstruation

mesenchymal referring to cells of the embryonic mesoderm that give rise to connective tissue, blood cells, blood vessels, lymphatic cells, and reticuloendothelial cells

mesenchymoma a mixed mesenchymal tumor composed of several cellular elements, excluding fibrous tissue

mesentery in the lining of the abdominal cavity, a fold that attaches the small intestine to the posterior abdominal wall by which the viscera are supported

mesothelioma tumors of the lining of the chest or abdomen

meta- in chemistry, a prefix denoting that a compound is formed by two substitutions in the benzene ring separated by one carbon atom, i.e., linked to the first and third, second and fourth, etc., carbon atoms of the ring; usually abbreviated *m-*

meta-analysis pooled statistical analysis of several similar studies

metabolism the whole range of biochemical processes that occur within living organisms, consisting both of anabolism and catabolism (the buildup and breakdown of substances, respectively)

metabolite a substance produced by metabolism

metaplasia a change in morphology of one differentiated cell type to a differentiated cell type that does not normally occur in that tissue

metastasis the appearance of a neoplasm in a part of the body remote from the site of its origin

methemoglobin a compound formed from hemoglobin by oxidation of the iron atom from the ferrous (Fe²⁺) to the ferric (Fe³⁺) state with essentially ionic bonds, rendering it incapable of functioning reversibly as an oxygen carrier; methemoglobin is present in small amounts in blood normally, but injury or toxic agents can increase the conversion

microbe a microorganism; microbes include bacteria, fungi, and protozoa

microglioma an intracranial neoplasm of microglial cell origin that is structurally similar to reticulum cell sarcoma

micronucleus nucleus separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes; the plural is micronuclei

microsome fragmented endoplasmic reticulum containing ribosomes formed from sheared eukaryotic cells; contain cytochrome P450

mineral wool may refer to either slag wool or rock wool depending on the raw material from which it is produced

miscible capable of being mixed without separation into distinct components

mitogen a substance that induces mitosis

mitosis process of cell reproduction consisting of a sequence of modifications of the nucleus that result in the formation of two daughter cells with exactly the same chromosome and DNA content as that of the original cell

molecular weight the molecular weight of a substance is the weight in atomic mass units of all the atoms in a given molecular formula

molluscicide pesticide used against mollusks, which usually is used in agriculture or gardening to control gastropod pests like slugs and snails that can damage crops by feeding on them

monocyte a mononuclear phagocytic leukocyte

monomer a chemical subunit that is joined to other similar subunits so as to produce a polymer

multiple myeloma cancer of leukocytes (plasma cells) in the bone marrow; bone-marrow cancer

mutagen any agent that causes the production of a mutation

mutagenicity the capability to induce mutation, or permanent change, in genetic material

myasthenia gravis a neurological disorder causing muscular weakness and fatigue, especially in the face, eyes, lips, tongue, throat, and neck

mycosis fungoides a rare, chronic, malignant T-cell lymphoma, first of the skin and in later stages of the lymph nodes and internal organs

myelocytic leukemia a leukemia arising from non-lymphocyte white blood cells in the bone marrow

myelodysplastic syndromes a group of clonal stem cell disorders associated with defects in cell differentiation, ineffective hematopoiesis, and associated cytopenias; may further develop into acute myelogenous leukemia

myeloid pertaining to or derived from cells of myeloid lineage of the bone marrow, such as red blood cells, monocytes, granulocytes, and platelets; sometimes used with reference to the spinal cord

myeloid leukemia a heterogeneous group of neoplasms that originate from hematopoietic progenitor cells of the myeloid lineage (red blood cells, monocytes, granulocytes, and platelets)

myeloma a tumor composed of cells normally found in the bone marrow

N

nasal cavity air-filled space above and behind the nose

nasal turbinates (nasal conchae, nasoturbinates) scrolled spongy bones in the posterior part of the nasal cavity

nasopharynx the upper part of the pharynx, posterior to the nasal cavity and above the soft palate

National Priorities List (NPL) a list of hazardous waste sites eligible for long-term remedial action financed under the U.S. EPA Superfund program; EPA regulations outline a formal process for assessing hazardous waste sites and placing them on the NPL

necrosis the pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage and which does not require energy to proceed, as opposed to apoptosis which does require energy

neonatal relating to or affecting the first four weeks after birth

neoplasia abnormal proliferation of cells

neoplasm an abnormal group of cells; a tumor

neoplastic pertaining to new and abnormal cell growth

nephroblastoma see Wilms' tumor

nephrotic syndrome a kidney disorder characterized by swelling, excessive proteins in the urine, and extreme susceptibility to infections

neural pertaining to the nerves

neuroblastoma a malignant tumor of the nervous system occurring chiefly in infants and young children

neurogenic 1. originating in the nervous tissue 2. forming nervous tissue

neutrophil a granular leukocyte having a nucleus with three to five lobes connected by slender threads of chromatin

nodule a swelling or protuberance

non-Hodgkin's lymphoma a heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin's disease

nucleic acid a polymer of nucleotides in which the phosphate of one of the repeating nucleotide subunits is linked to the sugar of the adjacent one; functions in the storage and transmission of genetic information and is found in chromosomes, nucleoli, mitochondria, and cytoplasm of all cells and in viruses

nucleotide the molecular subunit of nucleic acids; consists of a purine or pyrimidine base, a sugar, and phosphoric acid

nucleus a large spherical or oval, membrane-bound cell organelle present in most cells; contains most of the cell's DNA and some of its RNA

O

oat-cell carcinoma (also called small-cell carcinoma or small-cell bronchogenic carcinoma) a type of lung cancer

octanol-water partition coefficient (K_{ow}) a measure of the equilibrium concentration of a compound between octanol and water

odds ratio a way of comparing whether the probability of a certain event is the same for two groups; it is often used as a statistical measure of the likelihood of developing a disease given a certain factor, such as exposure to an agent

odontoma a benign tumor consisting of cementum, dentin, enamel, and pulp tissue that may form anomalous miniature teeth

offgassing the release of gaseous chemicals from a solid material

olfactory nerves the nerves associated with the sense of smell

oligodendroglioma a neoplasm derived from oligodendrocytes (glial cells of the central nervous system which wrap around individual nerve axons to form a myelin sheath)

oncogenes genes associated with cancer; malignant transformation of tissue appears to be associated with either the turning-on of these genes, or an increase in the rate at which they form their specific proteins

oncogenicity the capacity to induce tumors

optical rotation rotation of the plane of polarization of plane-polarized light, or of the major axis of the polarization ellipse of elliptically polarized light by transmission through a substance or medium

oral administration administration of a drug or test substance via the mouth

oral cavity the cavity of the mouth, bounded above by the hard and soft palates and below by the tongue and the mucous membrane connecting it with the inner part of the mandible

organic in chemistry, relates to the chemistry of the compounds of carbon

oropharynx soft palate, tonsils, and back of the tongue and throat

ortho- in chemistry, denoting that a compound has two substitutions on adjacent carbon atoms in a benzene ring; usually abbreviated *o-*

osteoporosis an abnormal loss of bone substance

ovary one of the two female reproductive organs in which eggs are formed

ovulation the discharge of an egg from an ovary

oxidant the substance that is reduced and that, therefore, oxidizes the other component of an oxidation-reduction system

oxidase one of a group of enzymes now termed oxidoreductases that bring about oxidation by the addition of oxygen to a metabolite or by the removal of hydrogen or of one or more electrons

oxidation chemical reaction that causes the loss of electrons, usually involving the addition of oxygen to a chemical; always occurs accompanied by reduction

oxidize to lose electrons, which usually causes a chemical to combine with oxygen

P

palate the partition separating the nasal and oral cavities

pancreas a large gland behind the stomach that secretes both hormones and enzymes involved in digestion and metabolism

papilloma a benign tumor derived from epithelium that can arise from skin, mucous membranes, or glandular ducts and projects from the surrounding surface

para- in chemistry, a prefix designating two substitutions in the benzene ring arranged symmetrically, i.e., linked to opposite carbon atoms in the ring; usually abbreviated *p-*

paraformaldehyde a polymer of formaldehyde

paranasal alongside the nose

paranasal sinuses air-filled cavities surrounding the nasal cavity; there are 4 pairs of paranasal sinuses: maxillary, frontal, ethmoid, and sphenoid

parathyroid gland any of four small glands situated beside the thyroid gland

parenchyma the distinguishing or specific cells of a gland or organ, contained in and supported by the connective tissue, framework, or stroma

parenteral not through the alimentary (food) canal, but any subcutaneous, intramuscular, or intravenous injection, as well as through inhalation or contact with the skin

Parkinson's syndrome a neurological disease characterized by muscular rigidity, tremor, expressionless face, abnormal posture, and salivation

pars distalis the major portion of the anterior lobe of the pituitary gland

particulate fine liquid or solid particles such as dust, smoke, mist, fumes, or smog suspended in air or atmospheric emissions

pathologist an expert in pathology (the study of disease)

pathology the study of the nature of diseases, especially of the structural and functional changes in body tissues, organs, or fluids caused by disease, physical and biological agents, and toxic substances

pelvis the lower portion of the trunk of the body, bounded anteriorly and laterally by the two hipbones and posteriorly by the sacrum and coccyx; also, the funnel-shaped part of the kidney leading into the ureter

pemphigus diseases any of a group of chronic, relapsing autoimmune skin diseases that cause blisters and erosions of the skin and mucous membranes

perched aquifer an aquifer that has a confining layer below the groundwater and sits above the main water table

perinatal of, involving, or occurring during the period closely surrounding the time of birth

perirenal of, relating to, occurring in, or being the tissues surrounding the kidney

perithecium in fungi, a flask-shaped fruiting body, one of the many shapes that bear asci and ascospores, and that are used as an aid in identifying a fungus; the plural is perithecia

peritoneum the lining surrounding the abdominal cavity and containing the viscera (internal organs in the body's trunk)

permissible exposure limit (PEL) any of three OSHA-enforceable limits of airborne exposure to chemicals or particulates: 1. PEL-TWA (time-weighted average) — air concentration that must not be exceeded during any 8-hour work shift of a 40-hour work week; 2. PEL-STEL (short-term exposure limit) — air concentration that must not be exceeded during any 15-minute interval; and 3. PEL-C (ceiling) — air concentration that must never be exceeded, even for an instant

peroxide that oxide of any series that contains the greatest number of oxygen atoms; applied most correctly to compounds containing an -O-O- link, as in hydrogen peroxide (H-O-O-H)

peroxy- prefix denoting the presence of an extra O atom, as in peroxides, peroxy acids (e.g., hydrogen peroxide, peroxyformic acid)

pesticide as defined by the Federal Insecticide, Fungicide and Rodenticide Act, a pesticide includes any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest, any substance or mixture of substances intended for use as a plant regulator, defoliant, or desiccant, and any nitrogen stabilizer

petroleum distillate a material produced by a combination of vaporization and condensation of petroleum

pH a numeric scale of acidity and alkalinity, ranging from 0 to 14, that expresses the negative logarithm of the hydrogen ion concentration

phagocyte cells that ingest microorganisms, other cells, and foreign particles

phagocytosis the process of ingestion and digestion by cells of solid substances, such as other cells, bacteria, bits of necrosed tissue, or foreign particles

pharmacokinetics movements of drugs within biological systems, as affected by absorption, distribution, elimination, and biotransformation

pharynx the passageway connecting the oral and nasal cavities to the larynx and esophagus

phenotype in genetics, a category or group to which an individual may be assigned on the basis of one or more characteristics observable clinically or by laboratory means that reflect genetic variation or gene-environment interaction; a phenotype may include more than one genotype

pheochromocytoma (also called pheochromoblastoma) a neoplasm, usually benign, derived from cells in the adrenal medullary tissue

phlebotomy incision of a vein for the removal or withdrawal of blood

photodecomposition chemical breaking down by means of light

photolysis the decomposition or separation of molecules by the action of light

photosensitizers substances that sensitize an organism, cell, or tissue to light

pituitary gland a small gland at the base of the brain that secretes several important hormones

placenta the organ in most mammals that connects the fetus with the mother's uterus

plant extract material recovered from a plant usually by subjecting the plant to treatment(s) with a solvent such as water, alcohol, or ether

plasma the fluid part of blood or lymph, as distinguished from suspended material (red and white blood cells); blood plasma contains platelets and clotting factors

platelet an irregularly shaped disk-like fragment of megakaryocytes found in blood that has a major role in clotting; it is about one-third to one-half the size of an erythrocyte, and contains no hemoglobin or nucleus

pleomorphic occurring in various distinct forms

pleura pertaining to the membrane surrounding the lungs and lining the chest cavity

polycyclic containing more than one benzene ring in a condensed form

polycythemia vera a disease characterized by an absolute increase in red cell mass and total blood volume

polymer a chemical formed by the joining together of similar chemical subunits

polymorphism a variation in the DNA that is too common to be due merely to new mutation

polyp a protruding growth from mucous membrane

polypoid resembling a polyp

positive control in an experiment, an agent known to have a positive effect and used as a standard for measuring a tested substance's effect and to verify that the experiment is functioning correctly

postpartum occurring after childbirth

prenatal existing or occurring before birth

primary cancer the original cancer developed in an organism

primate any of an order of mammals including man, apes, monkeys, and related forms

progenitor cell a precursor cell, one which differentiates into other cell types

prokaryote a primarily unicellular microorganism that lacks a cell nucleus or any other membrane-bound organelles such as mitochondria; its genome consists of a single large molecule of DNA not enclosed within a membrane, and it does not undergo mitosis during replication

promoter a chemical that, though not carcinogenic itself, serves to dramatically potentiate the effect of a carcinogen

promyelocytic the developmental stage of a granular leukocyte between the myeloblast and myelocyte

prostate a gland in males that surrounds the neck of the urinary bladder and the urethra and secretes a milky fluid that is discharged at the time of emission of semen

psoriasis a chronic, hereditary, recurrent skin disease characterized by bright red elevations covered with silvery scales

pulmonary of or relating to the lungs

pyrolysis decomposition of a substance by heat in the absence of air

pyrrole a heterocyclic aromatic organic compound consisting of a five-membered ring with four carbon and one nitrogen atoms

Q

quaternary in chemistry, the term describes a substance with four chemical groups attached to a central atom; when the central atom is a trivalent nitrogen atom (N), adding the fourth group places a positive charge on N and compounds thus formed are called quaternary ammonium compounds

R

R- designation of a particular enantiomer of a stereoisomeric chemical, similar to D- and L-, but instead of being determined by rotating planes of polarized light, it is determined by the chemical structure

racemic denoting a mixture that is optically inactive, being composed of an equal number of dextro- and levorotary substances (see DL-)

radioactive having the property of emitting radiation (such as alpha, beta, or neutron particles or gamma rays) from an atomic nucleus

radiotherapy the treatment of disease by means of radioactive emissions or materials

renal pertaining to the kidney

reportable quantity (RQ) under CERCLA and EPCRA, the quantity of a hazardous substance that triggers mandatory immediate reports to the National Response Center, State Emergency Response Commissions, and Local Emergency Planning Committees if equaled or exceeded in releases to the environment; certain exemptions are listed in 40 CFR 302.6

resin any of a class of solid or semisolid viscous substances obtained either as exudations from certain plants or prepared by polymerization of simple molecules

respirability the relative amount of airborne particles or fibers reaching the alveolar region of the lung

respirable fiber fibers that can reach the deepest part of the lung; respirable fibers usually are defined as particles with an aerodynamic diameter less than 3 μm and length greater than 5 μm and with an aspect ratio of greater than 3:1

respirable fraction that portion of dust or fibers that can reach the alveolar or gas exchange region of the respiratory system

respiratory tract the structures and organs involved in breathing; includes the upper respiratory tract (nose, pharynx, larynx) and lower respiratory tract (trachea and lungs [bronchi, bronchioles, alveoli])

reticulum cell a cell in the reticuloendothelial system (also called the mononuclear phagocytic system and lymphoreticular system) that has endothelial and reticular attributes; the cells are primarily macrophages and monocytes found in the spleen and lymph nodes, Kupffer cells in the liver, and histiocytes found in tissue

retrospective study an epidemiological study that collects information about past events that may be related to the present distribution of disease

rhabdomyosarcoma malignant tumor of striated muscle cells

rheumatoid arthritis a chronic disease of the joints, marked by inflammatory changes of joint structures

rhinitis inflammation of the mucous membrane of the nose

rodenticide any substance or mixture of substances used to kill rodents or to prevent them from damaging food, crops, etc.

S

S- designation of a particular enantiomer of a stereoisomeric chemical similar to D- and L-, but instead of being determined by rotating plane polarized light, it is determined by the chemical structure

salivary gland any of several exocrine glands in the mouth that secrete saliva, a fluid that keeps the mouth moist and aids in digestion

sarcoma a malignant neoplasm derived from connective tissue

schwannoma a peripheral glioma originating from schwann cells

scleroderma a chronic hardening and shrinking of connective tissue; affects such parts of the body as the skin, heart, esophagus, kidneys, and lungs

scrotum the pouch that contains the testes and their accessory organs

sebaceous referring to a gland in the skin which forms an oily secretion into the hair follicle near the surface of the skin

secondary cancer a cancer arising through metastasis of primary cancer

sedative an agent that relieves excitement or anxiety and induces sleep

sensitizer a substance that initiates the process of developing an allergic response to that substance on subsequent exposures

sinonasal pertaining to the nasal and sinus cavities

sintering forming a coherent bonded mass by heating metal powders without melting

sister chromatid exchange the exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors

small intestine the smaller diameter tube of the intestine, about 20 feet long, extending from the opening of the stomach to the large intestine

smelter an establishment used to separate or refine a metal from its ore, often with accompanying chemical change

solubility the ability of a substance to dissolve in another substance and form a solution

soluble capable of being dissolved; able to pass into solution in a particular solvent such as water, alcohol, or oil, and form a clear mixture

somatic affecting or characteristic of the body as opposed to the mind or spirit; somatic chromosomes include the non-sex chromosomes

SOS chromotest a bacterial test for detecting DNA-damaging agents consisting of a colorimetric assay based on the induction by these agents of the SOS function *sfIA*, whose level of expression is monitored by means of a *sfIA::lacZ* operon fusion; the name SOS for this repair process is based on its nature as a response to distress (analogous to the SOS signal in Morse code)

specific gravity the ratio of the density of a substance to the density of a standard substance; for liquids and solids the standard substance is usually water, for gases the standard substance is air

spindle cell a cell that is tapered at both ends

spleen a large, vascular, lymphatic organ in the upper abdominal cavity that stores blood cells, removes worn out red blood cells and other debris, and serves to initiate immune responses to antigens circulating in the blood

squamous cell thin, flat epithelial or endothelial cell; multiple layers of squamous cells are called stratified squamous cells

standardized incidence ratio (SIR) the ratio of observed to expected new incidences of a specific health outcome (e.g., cancer); the figure for expected incidence reflects the number of incidences for the larger population from which the study sample has been taken, e.g., national level incidences

standardized mortality ratio (SMR) the ratio of observed to expected deaths to a specific health outcome (e.g., cancer); the figure for expected deaths reflects the number of deaths for the larger population from which the study sample has been taken, e.g., national level of mortality attributed to a particular health outcome

stereoisomer a molecule containing the same number and kind of atom groupings as another but in a different arrangement in space, by virtue of which it exhibits different properties

steroid hormone any of the various hormones secreted by the adrenal cortex, testes, ovaries, and placenta

stromal referring to the supporting tissue of an organ, as opposed to the parenchyma, the functional portion of an organ

subacute denoting the course of a disease of moderate duration or severity (i.e., between acute and chronic); in rodent testing, usually pertains to a dosing schedule of less than one month

subchronic in rodent testing, generally refers to a dosing schedule lasting from one to three months

subcutaneous beneath the skin

subcutaneous injection injection beneath the skin

synergism the aspect of two agents interacting to produce an effect greater than the sum of the agents' individual effects

T

target organ the organ affected by a specific chemical in a specific species

technical grade a purity standard applied to a chemical that may contain multiple impurities

teratogen a drug or other agent that causes abnormal development

teratology the study of malformation or serious deviations from the normal development of organisms

testes the male gonads; they are situated in the scrotum and they produce sperm and the male sex hormone testosterone

thorax the part of the body that lies between the neck and the respiratory diaphragm and that is encased by ribs; the chest

threshold limit value (TLV) the maximum permissible concentration of a material, generally expressed in parts per million in air for some defined period of time

thymus a lymphoid gland located in the upper chest or the base of the neck and serving to help in developing the T-cell component of the adaptive immune system of most young vertebrates

thyroid gland a large gland situated at the base of the neck and producing hormones that are involved in regulating the rate of metabolism

time-weighted average (TWA) the average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration)

topical designed for direct application to a specific part of the body

toxemia the condition resulting from the spread of bacterial products (toxins) by the blood stream

toxic of or pertaining to a poison

trachea (also called the windpipe) the cartilage-ringed tube that connects the larynx and bronchi

transgenic an animal that carries a foreign gene that has been deliberately inserted into its genome

transplacental through the placenta

trichofolliculoma a benign, usually solitary, dome-shaped nodular lesion with a central pore that frequently contains a woolly hair-like tuft; usually occurs on the head or neck and derived from a hair follicle

trioxane a trimer of formaldehyde used as fuel and in plastics manufacture

tuberculosis a communicable disease caused by bacteria and principally affecting the lungs

tubular cell a cell which has a tubule or small tube-like structure

tumor growth of abnormal tissue resulting from excessive cell division; also called a neoplasm

tumorigenic causing or producing tumors

tunica albuginea a dense white fibrous sheath that encloses a part or organ, such as the testicle or ovary

tunica vaginalis serous membrane that covers the testis and duct leading out of the testis

U

ubiquitous present everywhere at once

ulcerative colitis the chronic, recurrent breaking of tissue in the colon, with such symptoms as abdominal pain and rectal bleeding

unpigmented schwannoma a neoplasm of a Schwann cell (a cell which wraps around the axon of peripheral nerves forming a myelin sheath), that does not contain granules of melanin, melanosomes, and is usually benign

upper respiratory tract consists of the nasal and oral cavities, pharynx, larynx, and trachea

urinary bladder the sac, situated in the front pelvic area, that serves as a reservoir for urine

urinary tract the organs and ducts involved in producing and eliminating urine

urothelial pertaining to the urothelium, the lining of the urinary tract, including the renal pelvis, ureters, urinary bladder, and urethra

urticaria (also called hives) a vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated patches (wheals) and often attended by severe itching

uterus in female animals, the hollow muscular organ in which the developing embryo and fetus lives and is nourished

V

vagina the passage leading from the uterus to the outside of the female body

vaginal trichomoniasis an infection of the vagina caused by a microorganism and involving vaginal discharge that is difficult to treat

valence a numerical measure of combining capacity of an atom/ion with other atoms/ions to form chemical bonds; valence is the relative combining capacity with respect to that of the standard hydrogen atom (valence = 1) and depends on the electronic configuration of the atoms

vapor density the ratio of the weight of a given volume of one gas to the weight of an equal volume of another gas at the same temperature and pressure

vapor density, relative a value that indicates how many times a gas (or vapor) is heavier than air at the same temperature; if the substance is a liquid or solid, the value applies only to the vapor formed from the boiling liquid

vapor pressure the pressure exerted by a vapor in equilibrium with its solid or liquid phase

vascular pertaining to vessels or ducts that convey fluids such as blood, lymph, or sap; in human or veterinary medicine, vascular pertains to blood vessels

vehicle the substance in which a compound is dissolved or mixed prior to an animal's being dosed with that compound

vesicant blister-inducing agent

viscera organs of the digestive, respiratory, urogenital, and endocrine systems, as well as the spleen, the heart, and great vessels

viscosity the resistance to flow

vitiligo an autoimmune disorder in which areas on various parts of the skin are depigmented from the loss of melanocytes

W

Wegener's granulomatosis a progressive disease characterized by tumor-like lesions of the respiratory tract, inflammation of the minute branches of the arteries, and, in the later stages, inflammation of all the organs of the body

Weston cells a standard voltaic cell (trademark Weston) producing a constant and accurately known electromotive force that can be used to calibrate voltage-measuring instruments

white pulp a minor portion of the spleen, which is composed of lymphocytes and may form germinal centers, which serve an immune function similar to the follicles of lymph nodes

Wilms' tumor a rapidly developing malignant tumor of the kidneys, usually affecting children under age five

X

xenobiotic a pharmacologically, endocrinologically, or toxicologically active substance not endogenously produced and therefore foreign to an organism

Z

Zymbal gland any of several sebaceous glands surrounding the external ear canal in rodents

Acronyms and Abbreviations

A	adenine	IARC	International Agency for Research on Cancer
AA	aristolochic acid	IDLH	immediately dangerous to life and health
AAN	aristolochic acid nephropathy	IgG	immunoglobulin G
ACGIH	American Conference of Governmental Industrial Hygienists	IL	interleukin
ADH	alcohol dehydrogenase	IL-3	interleukin-3
ATSDR	Agency for Toxic Substances and Disease Registry	ISO	International Organization for Standardization
BEN	Balkan endemic nephropathy	JM	Johns Manville
BRCA	breast cancer susceptibility proteins	K_{dis}	dissolution rate
C	cytosine	K_{ow}	octanol-water partition coefficient
CAS	Chemical Abstracts Service	LET	linear energy transfer
CAS No.	Chemical Abstracts Service Registry number	MCA 38	murine colon adenocarcinoma cell line
CDC	Centers for Disease Control and Prevention	MCL	maximum contaminant level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act	min	minute(s)
CERHR	Center for Evaluation of Risks to Human Reproduction	MMVF	man-made (or machine-made) vitreous fibers
CFR	Code of Federal Regulations	mol wt	molecular weight
CHO	Chinese hamster ovary	N/A	not applicable
CI	confidence interval	NADPH	nicotinamide adenine dinucleotide phosphate, reduced form
C.I.	Colour Index	NAICS	North American Industrial Classification System
COX	cyclooxygenase	NCI	National Cancer Institute
CPSC	Consumer Product Safety Commission	NHANES	National Health and Nutrition Examination Survey
CYP	cytochrome P450	NIEHS	National Institute of Environmental Health Sciences
2,4-D	2,4-dichlorophenoxyacetic acid	NIH	National Institutes of Health
dA-AAI	7-(deoxyadenosin- <i>N</i> 6-yl)-aristolactam I	NIOSH	National Institute for Occupational Safety and Health
dA-AAII	7-(deoxyadenosin- <i>N</i> 6-yl)-aristolactam II	NNK	4-(<i>N</i> -nitrosomethylamino)-1-(3-pyridyl)-1-butanone
DDD	1,1-dichloro-2,2-bis(<i>p</i> -chlorophenyl)ethane	NNN	<i>N</i> -nitrosornicotine
DDE	1,1-dichloro-2,2-bis(<i>p</i> -chlorophenyl)ethylene	No.	number
DDT	dichlorodiphenyltrichloroethane	NOHS	National Occupational Hazard Survey
dec	decomposes (used to indicate when a substance decomposes at its boiling point or melting point)	NR	not reported
dG	deoxyguanosine	NRC	Nuclear Regulatory Commission
dG-AAI	7-(deoxyguanosin- <i>N</i> 2-yl)-aristolactam I	NTP	National Toxicology Program
dG-AAII	7-(deoxyguanosin- <i>N</i> 2-yl)-aristolactam II	OR	odds ratio
DHHS	Department of Health and Human Services	OSHA	Occupational Safety and Health Administration
DHP	dihydropyrrrolizine	PAH	polycyclic aromatic hydrocarbon
DMDTC	dimethyldithiocarbamate	PEL	permissible exposure limit
DNA	deoxyribonucleic acid	PHS	Public Health Service
DNT	dinitrotoluene	pK_b	dissociation constant
DOE	Department of Energy, United States	PVC	polyvinyl chloride
DOT	Department of Transportation, United States	<i>r</i>	correlation coefficient
ed.	edition, editor(s)	r^2	coefficient of determination, a statistical measure of goodness of fit of a model
EPA	Environmental Protection Agency, United States	<i>R</i> -DHP	<i>R</i> -dihydropyrrrolizine, also called dehydroretrotronecine
EPCRA	Emergency Planning and Community Right-to-Know Act	REL	recommended exposure limit
F344	Fischer 344 (rats)	RNA	ribonucleic acid
FANC	Fanconi anemia complementation group proteins	RoC	Report on Carcinogens
FDA	Food and Drug Administration, United States	ROS	reactive oxygen species
FEMA	Federal Emergency Management Agency	RQ	reportable quantity
G	guanine	RR	relative risk (risk ratio or rate ratio)
GST	glutathione- <i>S</i> -transferase	<i>s</i>	second
GST-P+	glutathione <i>S</i> -transferase placental form positive	S&S	Schleicher & Schuell
h	hour(s)	<i>S</i> -DHP	<i>S</i> -dihydropyrrrolizine, also called dehydroheliotridine
HBeAg	hepatitis B e antigen	SIR	standardized incidence ratio
HBsAg	hepatitis B surface antigen	SMR	standardized mortality ratio
HCA	heterocyclic amine	spp.	species (plural)
HIV	human immunodeficiency virus	STEL	short-term exposure limit
HPLC	high performance liquid chromatography	suppl.	supplement
HUD	Housing and Urban Development	T	thymine
		TCLP	toxicity characteristic leaching procedure
		TLV	threshold-limit value
		TNT	trinitrotoluene
		TPQ	threshold planning quantity
		TRI	Toxics Release Inventory

TSCA	Toxic Substances Control Act
TSNA	tobacco-specific nitrosamine(s)
TWA	time-weighted average
USDA	United States Department of Agriculture
UV	ultraviolet
UVR	ultraviolet radiation
VOC	volatile organic chemical
vol.	volume
v/v	volume-volume ratio
WC	tungsten carbide
WHO	World Health Organization
wt.	weight
yr	year

Units of Measurement

Weight/Mass

Da	dalton	1 Da	= 1.65×10^{-24} g
g	gram	1 g	= 0.3035 oz (avoirdupois)
kg	kilogram	1 kg	= 2.2 lb
Mg	megagram, metric ton	1 Mg	= 10^6 g or 2,205 lb
μ g	microgram	1 μ g	= 10^{-6} g
mg	milligram	1 mg	= 1/1,000 g; 10^{-3} g
mol	mole	1 mol	= molecular weight in grams
ng	nanogram	1 ng	= 10^{-9} g
oz	ounce (avoirdupois)	1 oz	= 28.3 g
pg	picogram	1 pg	= 10^{-12} g
lb	pound	1 lb	= 0.45 kg

Length

cm	centimeter	100 cm	= 1 m
dm	decimeter	1 dm	= 1/10 m
ft	foot	1 ft	= 0.3 m
in.	inch	1 in.	= 2.54 cm
km	kilometer	1 km	= 0.6 mi
m	meter	1 m	= 3.3 ft
μ m	micrometer, micron	1 μ m	= 10^{-6} m
mi	mile	1 mi	= 1.6 km
mm	millimeter	1 mm	= 1/1,000 m; 10^{-3} m

Area

A	acre	1 A	= 4047 m ²
Ha	hectare	1 Ha	= 2.47 A
m ²	square meter	1 m ²	= 10.8 ft ²

Volume

ft ³	cubic foot	1 ft ³	= 0.028 m ³
m ³	cubic meter	1 m ³	= 35 cubic feet
cm ³ or cc	cubic centimeter	1 cc	= approximately 1 mL
gal	gallon (U.S.)	1 gal	= 3.8 L
L	liter	1 L	= 1.05 liquid quarts
mL	milliliter	1 mL	= 10^{-3} L

Concentration

mg/m ³	milligrams per cubic meter	1 mg/m ³	= (mol wt)(ppm)/24.45
mM	millimolar	1 mM	= 1 M/1,000
mppcf	millions of particles per cubic foot	mppcf \times 35.3	= millions of particles/m ³
M	molar; moles of solute per liter of solution		
N	normal; 1 gram equivalent of solute per liter of solution		
ppm	parts per million	1 ppm	= 1 mg/kg = (mg/m ³)(24.45)/(mol wt)
ppb	parts per billion	1 ppb	= 1 μ g/kg
ppt	parts per trillion	1 ppt	= 1 ng/kg

Pressure

kPa	kilopascal	1 kPa	= 0.145 lb/in ²
MPa	megapascal	1 MPa	= 1 Pa \times 10^6
mm Hg	millimeter of mercury	1 mm Hg	= 0.0193 lb/in ²
Pa	pascal	1 Pa	= 1 newton per square meter

Temperature

$^{\circ}$ C	degrees Celsius	= ($^{\circ}$ F - 32) \times 5/9
$^{\circ}$ F	degrees Fahrenheit	= ($^{\circ}$ C \times 9/5) + 32

Energy/Power

A	ampere	1 A	= 1 C per second
C	coulomb	1 C	= 1 A \times s
eV	electronvolt	1 eV	= 1.6×10^{-12} erg
	erg	1 erg	= 10^{-7} J
J	joule	1 J	= 10^7 erg
keV	kiloelectronvolt	1 keV	= 1,000 eV
MeV	megaelectronvolt	1 MeV	= 1×10^6 eV
mW	milliwatt	1 mW	= 10^4 erg/s

Radiation

Bq	becquerel	1 Bq	= 1 disintegration per second
Ci	curie	1 Ci	= 3.7×10^{10} disintegrations per second
Gy	gray	1 Gy	= 1 J per kg
mCi	millicurie	1 mCi	= 10^{-3} Ci
pCi	picocurie	1 pCi	= 10^{-12} Ci
	rad	1 rad	= 0.01 Gy
R	roentgen	1 R	= 2.58×10^{-4} C per kg
rem	roentgen equivalent man	1 rem	= 0.01 Sv
Sv	sievert	1 Sv	= 1 J per kg

Exponentials (Scientific Notation)

10^2 , 10^3 , 10^6 , etc.: superscripts refer to the number of times 10 is multiplied by itself, e.g., $10^2 = 10 \times 10 = 100$; $10^3 = 10 \times 10 \times 10 = 1,000$, etc.

Report on Carcinogens

Appendix A
Manufacturing Processes, Occupations, and Exposure Circumstances
Classified by IARC as Category 1, Carcinogenic to Humans

Appendix B
Substances Delisted from the Report on Carcinogens

Appendix C
Substances Reviewed but Not Recommended for Listing
in the Report on Carcinogens

Appendix D
List of Participants

Appendix E
Chemicals Nominated to the NTP in Fiscal Years 2004 to 2009 for
In-Depth Toxicological Evaluation

Appendix F
Substance Names and Common Synonyms

Appendix G
List of Substances by CAS Number

Appendix A: Manufacturing Processes, Occupations, and Exposure Circumstances Classified By IARC As Category 1, Carcinogenic To Humans

Certain manufacturing processes, occupations, and exposure circumstances have been considered by the International Agency for Research on Cancer (IARC) and have been classified by IARC as sources which are known to be carcinogenic to humans because of the associated increased incidences of cancer in workers in these settings. The NTP has not reviewed the data supporting the listings of these occupational situations or exposure circumstances as posing a carcinogenic threat to humans, and recognizes that certain aspects of these exposures may differ in different parts of the world or may have changed over time. In addition, the manufacturing processes and occupations reviewed by IARC in its determinations may differ greatly from what has been or is currently used in the United States. In the interest of public health and for completeness, these occupational exposures and exposure circumstances are referenced here with the corresponding IARC citation given. The interested reader is referred to these documents for details.

- Aluminum Production (IARC vol. 34, 1984, IARC suppl. 7, 1987)
- Auramine Manufacture (IARC vol. 1, 1972, IARC suppl. 4, 1982, IARC suppl. 7, 1987)
- Coal Gasification (IARC vol. 34, 1984, IARC suppl. 7, 1987)
- Coal, Indoor Emissions from Household Combustion of (IARC vol. 95, 2010)
- Coal-Tar Distillation (IARC vol. 92, 2010)

- Coke Production (IARC vol. 92, 2010)
- Hematite Mining (Underground) (IARC vol. 1, 1972, IARC suppl. 4, 1982, IARC suppl. 7, 1987)
- Iron and Steel Founding (Occupational Exposure during) (IARC vol. 34, 1984, IARC suppl. 7, 1987)
- Isopropyl Alcohol Manufacturing Using Strong Acids (IARC vol. 15, 1977, IARC suppl. 4, 1982, IARC suppl. 7, 1987)
- Magenta Manufacture (IARC vol. 57, 1993)
- Painter (Occupational Exposure as a) (IARC vol. 47, 1989)
- Rubber Manufacturing Industry (IARC suppl. 4, 1982, IARC vol. 28, 1982, IARC suppl. 7, 1987)

The following occupational exposure circumstances were previously listed by IARC as Group 1, but they are no longer considered by IARC as separate “agents.” IARC working groups for volume 100 (which reviewed all Group 1 carcinogens) concluded that the cancers observed in these industries were due to specific exposures, which are listed as Group 1 carcinogens:

- Boot and Shoe Manufacture and Repair (IARC vol. 25, 1981, IARC suppl. 4, 1982)
- Furniture Manufacture (IARC vol. 25, 1981, IARC suppl. 4, 1982, IARC suppl. 7, 1987)
- Nickel Refining (IARC vol. 2, 1973, IARC vol. 11, 1976, IARC suppl. 4, 1982).

Appendix B: Substances Delisted from the Report on Carcinogens

The agents, substances, mixtures or exposure circumstances contained in this appendix were previously listed in the Report on Carcinogens as either *known* or *reasonably anticipated to be human carcinogens*. For substances removed from the RoC prior to the 1996 establishment of a formal review procedure for delisting substances from the RoC, the table below shows the reason for delisting. The reason for delisting is in some cases the fact that residents of the United States are not exposed to these substances because since they are no longer produced or used in the United States and in other cases that the rulings or findings as to the carcinogenic potential of the substances have been revised (e.g., as a result of new studies). The table indicates the last edition of the RoC in which these substances appeared, to which reference can be made for all information available.

For each substance removed from the RoC as a result of a formal review for delisting (from the Eighth Edition forward), a profile is provided following the table, which summarizes the review for delisting, including the relevant information and the issues identified by the scientific review groups that led to the substance's delisting. Background documents outlining in more detail the issues considered during the reviews for delisting these substances can be obtained by contacting the National Toxicology Program at the following address: National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

Substance Name	CAS Number	Last Listing	Reason for Delisting
Chloramphenicol	56-75-7	<i>known</i> First RoC (1980)	Human data considered inadequate
Aramite	140-57-8	<i>reasonably anticipated</i> Fourth RoC (1985)	No U.S. residents exposed
<i>N,N</i> -Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)	494-03-1	<i>known</i> Fourth RoC (1985)	No U.S. residents exposed
Cycasin	14901-08-7	<i>reasonably anticipated</i> Fourth RoC (1985)	No U.S. residents exposed
Methyl iodide	78-88-4	<i>reasonably anticipated</i> Fourth RoC (1985)	Reevaluated by IARC; evidence now considered equivocal
5-Nitro- <i>o</i> -anisidine	99-59-2	<i>reasonably anticipated</i> Fifth RoC (1989)	Insufficient evidence of carcinogenicity
<i>p</i> -Nitrosodiphenylamine	156-10-5	<i>reasonably anticipated</i> Fifth RoC (1989)	Insufficient evidence of carcinogenicity
Ethyl acrylate	140-88-5	<i>reasonably anticipated</i> Eighth RoC (1998)	See following profile
Saccharin	81-07-2	<i>reasonably anticipated</i> Eighth RoC (1998)	See following profile

Report on Carcinogens Review Group Actions on the Nomination of Ethyl Acrylate for Delisting from the Report on Carcinogens

Summary of data contained in the Ethyl Acrylate Background Document (December 1998)

Ethyl Acrylate

CAS No. 140-88-5

Ethyl acrylate is used in various industries as an intermediate in the production of emulsion-based polymers which are then used in paint formulations, industrial coatings, and latex products. It is also used as a synthetic flavoring substance and fragrance adjuvant in consumer products. Human exposure to ethyl acrylate occurs mostly through inhalation of ethyl acrylate vapors, but it may also result from skin contact or ingestion as a food additive or by drinking contaminated water. The Report on Carcinogens review groups considered the data underlying the nomination to remove ethyl acrylate from the Report on Carcinogens where it has been listed as *reasonably anticipated to be a human carcinogen* since 1989. The basis for this listing was a gavage study which resulted in dose-related benign and malignant forestomach neoplasms in rats and mice. The Basic Acrylic Monomer Manufacturers, Inc. (BAMM), submitted a nomination to remove ethyl acrylate from the Report on Carcinogens based upon the following: (1) negative tumorigenicity results from chronic studies using routes other than gavage in corn oil, (2) research results suggesting that the forestomach carcinogenicity observed in the gavage studies was secondary to a site-specific and concentration-dependent irritating effect of ethyl acrylate, and (3) that significant human exposure to ethyl acrylate monomer is unlikely in light of current manufacturing practices and patterns of usage (see summary of ethyl acrylate carcinogenicity data below).

The majority opinion of the Report on Carcinogens review groups was to recommend that ethyl acrylate be removed from the Report on Carcinogens. This was based on the facts that (1) the forestomach tumors induced in animal studies were seen only when ethyl acrylate was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation, (2) animal studies by other routes of administration including inhalation were negative, and (3) because significant chronic human oral exposure to high concentrations of ethyl acrylate monomer is unlikely. Therefore ethyl acrylate does not meet the criteria to be listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*.

Summary of Available Carcinogenicity Data and Other Relevant Information

Cancer Studies in Experimental Animals

Although mutagenic in some *in vitro* tests, ethyl acrylate is not genotoxic under *in vivo* physiological conditions perhaps due to its rapid metabolism to acrylic acid and ethanol by carboxyesterases and detoxification through binding to non-protein sulfhydryls. Target tissue toxicity comprised of irritation has been observed in the skin in a lifetime mouse skin painting study, in the nasal olfactory mucosa in 27-month inhalation studies in rats and mice, and in the forestomach in two-year corn oil gavage studies in rats and mice. Only body weight reduction was observed in a two-year dosed-water study in rats. The forestomach carcinogenicity observed in the corn oil gavage studies represents the only treatment-related tumorigenic response in the various animal studies. The irritation, hyperplasia, and tumor

responses in the forestomach were related more to target tissue concentration of ethyl acrylate than to delivered dose in the chronic gavage study. Based upon stop-exposure studies, gavage doses of ethyl acrylate in corn oil sufficient to induce sustained mucosal hyperplasia in the forestomach must be administered for longer than six months to induce forestomach neoplasia.

Human Exposure and Cancer Studies in Humans

Prolonged consumer exposure to high levels of ethyl acrylate monomer by the oral route is unlikely. Potential significant exposures would most likely occur in an occupational setting where the routes of exposure would be dermal and/or inhalation. Ethyl acrylate has a strong acrid odor (odor threshold ~ 0.5 ppb) and is a known irritant to the skin, eyes, and mucous membranes, making it unlikely that humans would be chronically exposed to high concentrations. Data provided in the BAMM nomination on worker exposure show occupational exposure well below the threshold limit value (TLV=5 ppm for an eight-hour time-weighted average) and the short-term exposure limit (STEL=15 ppm), although exposure of painters in an unventilated room has been reported as high as 8 ppm in the painter's breathing zone.

An epidemiology study reported on mortality from cancer of the colon and rectum in three separate cohorts of workers from two plants manufacturing and polymerizing acrylate monomers. Workers were exposed to ethyl acrylate and methyl methacrylate monomer between 1933 and 1982. Risks for both types of cancer were associated with exposure in the earliest cohort, although the rectal cancer results are imprecise because of the small number of cases involved. The greatest relative risk was found in workers with the highest level of exposure and a 20 year latency. The other two cohorts, with later dates of hire, showed no excess risk, but very few cases were available for observation. This study, by itself, can neither establish nor rule out a causal relationship of ethyl acrylate with cancer.

Action On Nomination

Ethyl acrylate will be removed from the Report on Carcinogens because the relevant data are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This is based on the fact that the forestomach tumors induced in animal studies were seen only when the chemical was administered by gavage at high concentrations of ethyl acrylate, that induced marked local irritation and cellular proliferation, and because significant chronic human exposure to high concentrations of ethyl acrylate monomer is unlikely.

Report on Carcinogens Review Group Actions on the Nomination of Saccharin for Delisting from the Report on Carcinogens

Summary of data contained in the Saccharin Background Document (October 1997)

Saccharin

CAS No. 81-07-2

Saccharin and its sodium and potassium salts have been produced commercially in the United States for over 80 years. It is primarily used as a nonnutritive sweetening agent. Potential exposure to saccharin occurs through the consumption of dietetic foods and drinks and by use of some personal hygiene products. Potential exposure to saccharin also occurs in the workplace, specifically in occupations, industries, or facilities that produce and deal with saccharin and its salts. The Report on Carcinogens review groups considered the data

underlying the nomination to remove saccharin from the Report on Carcinogens where it has been listed as *reasonably anticipated to be a human carcinogen* since 1981. The basis for this listing was sufficient evidence of carcinogenicity in experimental animals. The Calorie Control Council submitted a nomination to the NTP to consider removing saccharin from the Report on Carcinogens based upon mechanistic data related to development of urinary bladder cancers in rats (see summary of saccharin carcinogenicity data below).

The majority opinion of the review groups was to recommend that saccharin be removed from the Report on Carcinogens. There is evidence for the carcinogenicity of saccharin in rats but less convincing evidence in mice. Studies indicate that the observed urinary bladder cancers in rats are related to the physiology of the rat urinary system including urinary pH, osmolality, volume, and the presence of precipitate, and urothelial damage with attendant hyperplasia following consumption of diets containing sodium saccharin at concentrations of 3% or higher with inconsistent findings at lower dietary concentrations. The factors thought to contribute to tumor induction by sodium saccharin in rats would not be expected to occur in humans. The mouse data are inconsistent and require verification by additional studies. Results of several epidemiology studies indicate no clear association between saccharin consumption and urinary bladder cancer. Although it is impossible to absolutely conclude that it poses no threat to human health, sodium saccharin is not *reasonably anticipated to be a human carcinogen* under conditions of general usage as an artificial sweetener.

Summary of Available Carcinogenicity Data and Other Relevant Information

Cancer Studies in Experimental Animals

In four studies of up to 30 months duration, sodium saccharin was carcinogenic in Charles River CD and Sprague-Dawley male rats as evidenced by a dose-related increased incidence of benign or malignant urinary bladder neoplasms at dietary concentrations greater than 1% (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Schoenig *et al.* 1985). Non-statistically significant increases in urinary bladder cancer have also been seen in saccharin-treated female rats from studies showing a positive effect in males (Arnold *et al.* 1980, Taylor *et al.* 1980). Furthermore, several initiation/promotion studies in different rat strains have shown a reduced latency and/or increased incidence of similar urinary bladder cancers in male and female rats fed sodium saccharin subsequent to treatment with different urinary bladder initiators (e.g., Hicks and Chowanec 1977, Cohen *et al.* 1979, Nakanishi *et al.* 1980a, West *et al.* 1986, Fukushima *et al.* 1990). Several additional rat studies in which sodium saccharin was administered either in the diet or in drinking water were negative for tumorigenicity (Fitzhugh *et al.* 1951, Lessel 1971, Schmähl 1973, Chowanec and Hicks 1979, Hooson *et al.* 1980, Schmähl and Habs 1984).

Three mouse studies have reported positive carcinogenicity following exposure to saccharin. Two of these studies involved surgical implantation of saccharin-containing cholesterol pellets into the urinary bladders and resulted in development of malignant urothelial neoplasms (Allen *et al.* 1957, Bryan *et al.* 1970). In the third study, dietary sodium saccharin resulted in increased incidences of malignant thyroid neoplasms (Prasad and Rai 1986). While the mouse data cannot be discounted, some of these studies had methodological flaws, provided limited information, did not show a dose-response, or had unexpected outcomes that may be species or strain-specific and should be verified by additional studies. Four studies in mice were judged negative for tumorigenesis (Roe *et al.* 1970, Kroes *et al.* 1977, Homberger 1978, Frederick *et al.* 1989) as were limited studies in nonhuman primates (McChesney *et al.* 1977 abstr., Sieber and

Adamson 1978, Thorgiersson *et al.* 1994, Cohen *et al.* 1996) and a single hamster study (Althoff *et al.* 1975).

Cancer Studies in Humans

Most of the relevant human epidemiology studies have examined associations between urinary bladder cancer and artificial sweeteners, rather than saccharin per se. The time trend data for bladder cancer show no clear indication that the increased use of saccharin or artificial sweeteners commencing in the 1940s is associated with a general increase in bladder cancer when controlled for confounding factors, chiefly smoking. Risks of bladder cancer in diabetics, who presumably consume greater amounts of artificial sweeteners compared to the general population, are not greater than risks in the general population (Armstrong and Doll 1975). Based upon several case-control studies there is no overall association of use of artificial sweeteners and bladder cancer (reviewed by IARC 1980, 1987b, JECEA 1993). However, an association between use of artificial sweeteners and bladder cancer cannot be ruled out in some case-control subgroups, albeit involving small numbers (Howe *et al.* 1980, Hoover and Strasser 1980, Cartwright *et al.* 1981, Morrison *et al.* 1982, Mommsen *et al.* 1983). Taken together, while the available epidemiology data show no consistent evidence that saccharin is associated with increased bladder cancer in general, a small increased risk in some subgroups, such as heavy users of artificial sweeteners, cannot be unequivocally excluded. With regard to the general population, if sodium saccharin is a risk factor, it is weak and cannot be proven or disproved due to lack of actual exposure data and intrinsic limitations of existing epidemiology studies.

Studies on Mechanisms of Carcinogenesis

Extensive studies of the mutagenicity and genotoxicity of saccharin have shown generally negative but occasionally conflicting results. Sodium saccharin is essentially nonmutagenic in conventional bacterial systems (reviewed by Ashby 1985, IARC 1987a,b, Whysner and Williams 1996) but is weakly clastogenic or genotoxic in short-term *in vitro* and in some *in vivo* test systems (reviewed by Ashby 1985, IARC 1987a,b, Whysner and Williams 1996). Urine from mice treated with sodium saccharin was mutagenic in the Ames test in one study (Batzinger *et al.* 1977). Saccharin does not covalently bind to DNA and does not induce unscheduled DNA synthesis in bladder urothelium.

Saccharin-induced carcinogenesis in rats shows a sex predilection for males (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980), an organ specificity for urinary bladder (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Fukushima *et al.* 1983, Schoenig *et al.* 1985), and a dose-response when exposure to dietary concentrations of 1 to 7.5% of the sodium salt of saccharin was begun early in life (beginning at birth or immediately at weaning) and continued for approximately two years (Schoenig *et al.* 1985). The results of mechanistic studies have shown that certain physiological conditions must be simultaneously or sequentially present for induction of urinary bladder tumorigenesis. These conditions include a urinary pH greater than 6.5, increased urinary sodium concentration, increased urine volume, decreased urine osmolality, presence of urinary crystals or precipitate, with resulting damage to the urothelium prompting a proliferative (hyperplastic) response of the urinary bladder epithelium. All of these conditions have been studied extensively in male rats but less so in females or in mice. The high levels of urinary protein characteristically produced by male rats may partially explain the sex predilection. The high intrinsic rate of urothelial proliferation at about the time of weaning is also believed to contribute to the observed tumorigenic effects. The urinary milieu in rats, especially male rats, is sufficiently different from that in humans or other species to sup-

port the contention that these observations are rat-specific. Pharmacokinetic and metabolism data on sodium saccharin do not explain the male rat sensitivity for induction of urinary bladder neoplasms (Sweetman and Renwick 1979, 1980).

Action On Nomination

Saccharin will be removed from the Report on Carcinogens, because the rodent cancer data are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This is based on the perception that the observed urinary-bladder tumors in rats arise by mechanisms not relevant to humans, and the lack of data in humans suggesting a carcinogenic hazard.

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Appendix C: Substances Reviewed but Not Recommended for Listing in the Report on Carcinogens

Nominated agents, substances, mixtures, or exposure circumstances all are considered for possible listing in the Report on Carcinogens. For many of these, it is possible to determine that there are insufficient data available to warrant any formal consideration by the scientific review groups without carrying out an extensive evaluation. For others, relevant animal or human cancer studies do exist, but, after a formal consideration, the review groups reach the conclusion that the data do not warrant listing the agent, substance, mixture, or exposure circumstance in the Report on Carcinogens. The following table

contains a record of nominations that were formally considered for listing by the NTP and, after evaluation by the Report on Carcinogens review groups, were recommended not to be listed in the Report on Carcinogens. Background documents outlining in more detail the issues considered during formal reviews of a nomination can be obtained by contacting the National Toxicology Program at the following address: National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

Substance Name	CAS Number	Reviewed for Listing in	Reason for not Listing
Methyl <i>tert</i> -butyl Ether (MTBE)	1634-04-4	Ninth RoC (1999)	Rodent cancer data not sufficient
Nickel Alloys		Tenth RoC (2000)	Human data are inadequate and rodent cancer data not sufficient
Diethanolamine	111-42-2	Eleventh RoC (2004)	Rodent cancer data not sufficient

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Appendix E: Chemicals Nominated to the NTP in Fiscal Years 2004 to 2009 for In-Depth Toxicological Evaluation

This table contains information updated through December 2009. If NTP testing has been conducted, a link is provided to the results and status information. For additional information about the NTP studies listed, contact Central Data Management, Mail Drop K2-05, NIEHS, P.O. Box 12233, Research Triangle Park, NC 27709 (Phone:

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Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Abscisic acid 14375-45-2	NCI 2004	A widely available plant hormone whose toxicological properties have not been thoroughly investigated • Genotoxicity testing	Selected http://ntp.niehs.nih.gov/go/ts-M040027
Acenaphthenequinone 82-86-0	Private individual 2005	• Initial toxicological characterization	In review/pending — see Polycyclic aromatic hydrocarbon quinones
Acesulfame potassium 55589-62-3	Private individual 2006	Widely used as a component of sweetener blends with Splenda and in artificially sweetened products such as "lite" fruit juices, fruit drinks, ice creams, flavored water and sports drinks Inadequate long-term animal testing Tests carried out to date do not give reasonable assurance that acesulfame potassium is "safe" • Two-year toxicity/carcinogenicity studies in rats and mice	In review/pending http://ntp.niehs.nih.gov/go/ts-M960069
Acetoin 513-86-0	United Food and Commercial Workers International Union 2006		Selected — see Artificial butter flavoring and constituents http://ntp.niehs.nih.gov/go/ts-M990018
Acetyl-L-carnitine/ α -Lipoic acid supplements	NCI 2005	Consumer exposure through increasing dietary supplement use Lack of adequate toxicological data • Subchronic toxicity studies (individual and combination studies)	Deferred Acetyl-L-carnitine hydrochloride (5080-50-2) http://ntp.niehs.nih.gov/go/ts-M050013 DL- α -Lipoic acid (1077-28-7) http://ntp.niehs.nih.gov/go/TS-M980033 α -Lipoic acid (62-46-40) http://ntp.niehs.nih.gov/go/TS-M050014
Acetyl-L-carnitine hydrochloride 5080-50-2	NCI 2005		Deferred — see Acetyl-L-carnitine/ α -Lipoic acid supplements http://ntp.niehs.nih.gov/go/ts-M050013
Alkylanilines	NIEHS 2008	Potential for human exposure from a variety of industrial and ambient sources Suspicion of toxicity based on chemical structure Insufficient data to characterize toxicity of this subclass • Initial toxicological characterization	Selected 2-Ethylaniline (578-54-1) http://ntp.niehs.nih.gov/go/TS-08029 3-Ethylaniline (587-02-0) http://ntp.niehs.nih.gov/go/TS-08030 3,5-Xylidine (108-69-0) http://ntp.niehs.nih.gov/go/TS-11430-P
Aminopyridines	NCI 2006	Animal and human studies have shown that the aminopyridines are acutely toxic compounds, partly due to its ability to block K ⁺ channels, causing convulsions, seizures, among other effects • Toxicological characterization including chronic toxicity and carcinogenicity studies • Short-term mechanistic studies • Comparative neurotoxicity studies	Selected 2-Aminopyridine (504-29-0) http://ntp.niehs.nih.gov/go/TS-M20139 3-Aminopyridine (462-08-8) http://ntp.niehs.nih.gov/go/TS-M060052 4-Aminopyridine (504-24-5) http://ntp.niehs.nih.gov/go/TS-M060053
3-Aminopyridine 462-08-8	NCI 2006		Selected — see Aminopyridines http://ntp.niehs.nih.gov/go/ts-M060052
2-Aminopyridine 504-29-0	NCI 2006		Selected — see Aminopyridines http://ntp.niehs.nih.gov/go/ts-M20139
4-Aminopyridine 504-24-5	NCI 2006		Selected — see Aminopyridines http://ntp.niehs.nih.gov/go/ts-M060053
Ammonium metavanadate 7803-55-6	NIEHS/NTP; EPA 2007		Selected — see Tetravalent and pentavalent vanadium compounds

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Anthraquinone 84-65-1	Chemical Products Corporation 2009	<ul style="list-style-type: none"> • Carcinogenicity • Test currently available form of anthraquinone 	In review/pending http://ntp.niehs.nih.gov/go/ts-84651 Previously tested — see NTP TR-494
Antimony trioxide 1309-64-4	NIEHS 2005	<ul style="list-style-type: none"> • Significant human exposure in occupational settings • Lack of adequate two-year exposure carcinogenicity studies • Carcinogenicity, toxicity, cardiotoxicity 	Selected http://ntp.niehs.nih.gov/go/ts-10676-V
Antimony trioxide 1309-64-4	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-10676-V
Arbutin 497-76-7	NIEHS 2004	<ul style="list-style-type: none"> • Consumer exposure through food, cosmetics and dietary supplements • Lack of adequate toxicological data • Suspicion of toxicity based on chemical structure • <i>In vitro</i> and <i>in vivo</i> metabolism/disposition • <i>In vitro</i> and <i>in vivo</i> genetic toxicity 	Selected http://ntp.niehs.nih.gov/go/ts-M040101
Artemisinin and derivatives	NIEHS 2004	<ul style="list-style-type: none"> • Increased use as medicinal and dietary supplement to treat malaria and prevent cancer • Toxicological characterization 	No testing
Artemisinin 63968-64-9	NIEHS 2004		See Artemisinin and derivatives
Artificial butter flavoring and constituents	United Food and Commercial Workers International Union 2007	<ul style="list-style-type: none"> • Several outbreaks of fatal lung disease have been documented among workers exposed to the vapors of butter flavoring in the manufacture of popcorn, the most prominent chemical exposures being from diacetyl and acetoin • The potency and severity of diacetyl has been demonstrated by short-term laboratory tests conducted by NIOSH • Toxicity, carcinogenicity by inhalation • Mechanistic studies 	Selected Acetoin (513-86-0) http://ntp.niehs.nih.gov/go/TS-M990018 2,3-Butanedione (431-03-8) http://ntp.niehs.nih.gov/go/TS-M940009
Autumn Sunset True Color Concentrate	FDA 2005		Selected — see Permanent makeup inks http://ntp.niehs.nih.gov/go/TS-M070050
Bentonite 1302-78-9	Private individual 2005	<ul style="list-style-type: none"> • Bentonite clay is being advertised as a healing substance that helps remove toxins from the body; ads suggest that it can be used externally as a clay poultice, mudpack or in the bath • Dermal toxicity 	In review/pending
7,12-Benzanthraquinone 2498-66-0	Private individual 2005		In review/pending — see Polycyclic aromatic hydrocarbon quinones
Benzoic acid 65-85-0	Private individual 2005		No testing — see Sodium benzoate and benzoic acid in Foray 48B insecticide http://ntp.niehs.nih.gov/go/ts-65850
2,6-Dichloro-1,4-benzoquinone 697-91-6	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
Trifluoromethylbenzene (Benzotrifluoride) 98-08-8	NCI 2006	<ul style="list-style-type: none"> • High production volume and increased use • Potential worker exposures • Lack of adequate toxicological data • Demonstrated toxicity in short-term studies 	Deferred http://ntp.niehs.nih.gov/go/ts-98088
Bisphenol A 80-05-7	Private individual 2006	<ul style="list-style-type: none"> • There is widespread exposure to low doses of bisphenol A • Additional studies on the low-dose reproductive effects of bisphenol A are needed • Developmental reproductive effects 	Selected http://ntp.niehs.nih.gov/go/ts-10034-Y
Bisphenol AF 1478-61-1	NIEHS 2008	<ul style="list-style-type: none"> • Moderate production and use in polymer synthesis • Short-term studies suggest potential for endocrine disruption and adverse reproductive effects • Similarity in structure and endocrine effects to bisphenol A • Moderate production and use in polymer synthesis • Comprehensive toxicological characterization 	Selected http://ntp.niehs.nih.gov/go/TS-08002
Bitter orange N/A	Private individual 2004		Selected — see Creatine, Bitter orange and Saw palmetto http://ntp.niehs.nih.gov/go/ts-M040019

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Brominated phenols	NIEHS 2004	Lack of chronic toxicity and carcinogenicity data for brominated phenols • Toxicological characterization	In review/pending 2-Bromophenol (95-56-7) 3-Bromophenol (591-20-8) 4-Bromophenol (106-41-2) 2,4-Dibromophenol (615-58-7) 2,6-Dibromophenol (608-33-3) 3,5-Dibromophenol (626-41-5) Pentabromophenol (608-71-9) http://ntp.niehs.nih.gov/go/TS-11300-K 2,3,4,6-Tetrabromophenol (14400-94-3)
4-Bromofluorobenzene 460-00-4	NIEHS 2004	High production volume and use Lack of adequate toxicological data Suspicion of toxicity based on chemical structure • Toxicological testing	Deferred
2-Bromophenol 95-56-7	NIEHS 2004		In review/pending — see Brominated phenols
3-Bromophenol 591-20-8	NIEHS 2004		In review/pending — see Brominated phenols
4-Bromophenol 106-41-2	NIEHS 2004		In review/pending — see Brominated phenols
2,3-Butanedione 431-03-8	United Food and Commercial Workers International Union 2006		Selected — see Artificial butter flavoring and constituents http://ntp.niehs.nih.gov/go/ts-M940009
Butterbur 90082-63-6	NIEHS 2009	Use as a dietary supplement and lack of toxicological data Suspicion of toxicity based on pharmacological activity of constituents Potential presence of hepatotoxic pyrrolizidine alkaloids • Comprehensive toxicological characterization	Selected
<i>tert</i> -Butylacrylamide 107-58-4	NCI 2006	High production volume Potential worker and consumer exposures Lack of adequate toxicological data Suspicion of toxicity based on chemical structure (1,6,7) • 90-day toxicity, chemical disposition/metabolism, genotoxicity studies	Selected http://ntp.niehs.nih.gov/go/ts-M060004
Butylated hydroxyanisole (BHA) 25013-16-5	Private individual 2005	Widely used preservative in pet foods Dogs were sickened when fed pet food in which BHA was over formulated or unevenly mixed Since previous toxicity studies were performed using beagles, the nominator would like non-lethal studies in young, light-colored coat dogs that appear to be particularly sensitive to the toxic effects from BHA • Metabolism/excretion, hepatic studies in dogs (not beagles)	In review/pending http://ntp.niehs.nih.gov/go/ts-M88172
Butyl benzyl phthalate 85-68-7	Center for the Evaluation of Risks to Human Reproduction 2006		In review/pending — see Mixture of anti-androgenic phthalates http://ntp.niehs.nih.gov/go/ts-10422-E
3-Butylidene-phthalide 551-08-6	Private individual 2008		Selected — see Dong quai (<i>Angelica sinensis</i> root (308068-61-3) and extract (299184-76-2))
<i>tert</i> -Butylphenyl diphenyl phosphate 56803-37-3	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-10978-T
<i>n</i> -Butyl- <i>p</i> -hydroxybenzoate (Butylparaben) 94-26-8	NIEHS 2004	Widespread use in foods, cosmetics, and pharmaceuticals Potential reproductive toxicant Lack of adequate toxicological data • Toxicological characterization including reproductive toxicity studies	Selected http://ntp.niehs.nih.gov/go/ts-M88007

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Celebrex and Bextra	Private individual 2005	Vioux, a popular drug used to treat arthritis, was removed from the market when it was discovered that it increased the risk of heart attack and stroke; two other COX-2 inhibitors, Celebrex and Bextra, should be studied to determine if they have similar side effects • Toxicity, including cardiotoxicity	In review/pending Celecoxib (Celebrex) (169590-42-5) Valdecoxib (Bextra) (181695-72-7)
Celecoxib (Celebrex) 169590-42-5	Private individual 2005		In review/pending — see Celebrex and Bextra
Ceric oxide 1306-38-3	NIEHS 2004	Widespread industrial use and potential for increasing exposure Demonstrated pulmonary toxicity Lack of toxicity data for nanoscale form • Toxicological characterization with chemical disposition/toxicokinetics and nanoscale studies	Deferred
2-Chloropropenal 683-51-2	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
<i>p</i> -Chlorobenzotrifluoride 98-56-6	Kowa American Corp. 2006	High production volume No workplace exposure standards Increasing industrial and potential consumer use as a VOC-exempt solvent Lack of chronic toxicity data • Toxicological characterization	Selected http://ntp.niehs.nih.gov/go/ts-10472-T
Corrosion inhibitors mixture	Private individual 2005	Lack of data related to the health effects caused by the exposure to corrosion inhibitor mixtures Most of the chemicals have been studied in isolation, and not as mixtures found in commercial products • Toxicity testing	In review/pending
Creatine, Bitter orange, and Saw palmetto	Private individual 2004	Consumer exposure through increasing dietary supplement use Suspicion of toxicity Lack of adequate toxicity data • Long-term studies	Bitter orange http://ntp.niehs.nih.gov/go/ts-M040019 Creatine monohydrate (6020-87-7) Saw palmetto extract (84604-15-9)
Creatine monohydrate 6020-87-7	Private individual 2004		In review/pending — see Creatine, Bitter orange and Saw palmetto
Crystalline silica 14808-60-7	Private individual 2009		In review/pending — see Silica, crystalline — quartz http://ntp.niehs.nih.gov/go/ts-M920041
Drinking water disinfection by-products (DBPs) New and Emerging Chemical Classes	Private individual 2009	Concern is primarily for carcinogenic potential • Toxicological characterization	In review/pending 2,6-Dichloro-1,4-benzoquinone (697-91-6) 2-Chloropropenal (683-51-2) Dichloroacetaldehyde (79-02-7) <i>N,N</i> -Dichlorohistamine (109241-52-3) 1,1-Dichloropropanone (513-88-2) 2,3-Dichloropropenenitrile (2601-89-0) 2,2-Dichloropropionitrile (594-40-1) <i>N</i> -Nitroso-3-methylindole (58567-91-2) 1,1,1-Trichloropropanone (918-00-3)
Decabromodiphenyl oxide 1163-19-5	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-10672-E
2,6-Diaminopyridine 141-86-6	NCI 2005	Moderate production and industrial use Lack of adequate toxicological data • <i>In vitro</i> mammalian genotoxicity studies, dermal absorption studies	Selected http://ntp.niehs.nih.gov/go/ts-M050015
2,4-Dibromophenol 615-58-7	NIEHS 2004		In review/pending — see Brominated phenols
2,6-Dibromophenol 608-33-3	NIEHS 2004		In review/pending — see Brominated phenols
3,5-Dibromophenol 626-41-5	NIEHS 2004		In review/pending — see Brominated phenols

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Dibutyl phthalate 84-74-2	Center for the Evaluation of Risks to Human Reproduction 2006		Selected — see Mixture of anti-androgenic phthalates http://ntp.niehs.nih.gov/go/ts-10987-X
Dichloroacetaldehyde 79-02-7	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
N,N-Dichlorohistamine 109241-52-3	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
2,4-Dichlorophenoxyacetic acid (2,4-D) 94-75-7	Private individual 2005	Concern about health-related effects of 2,4-D exposure from the use of lawn care products	In review/pending http://ntp.niehs.nih.gov/go/ts-10451-Y
1,3-Dichloro-2-propanol 96-23-1	NIEHS 2004	High production volume and use Occurrence in foods Reproductive toxicity and carcinogenicity demonstrated but not adequately characterized • Toxicological characterization, metabolism and disposition • Reproductive toxicity • Carcinogenicity	Selected http://ntp.niehs.nih.gov/go/ts-11538-C
1,1-Dichloropropanone 513-88-2	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
2,3-Dichloropropenenitrile 2601-89-0	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
2,2-Dichloropropionitrile 594-40-1	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
Di(2-ethylhexyl)phthalate (DEHP) 117-81-7	FDA 2004	Long-term risks associated with medical exposures of infants to DEHP have not been clearly elucidated Significant knowledge gaps on the toxicokinetics and effects in fetal and neonatal primates of intravenous DEHP exposure Further studies will better define risks and benefits of utilizing non-DEHP-containing products • Toxicokinetics, biotransformation, reproductive toxicity, developmental toxicity, immunotoxicity	In review/pending http://ntp.niehs.nih.gov/go/ts-10188-J
Di(2-ethylhexyl) phthalate 117-81-7	Center for the Evaluation of Risks to Human Reproduction 2006		Selected — see Mixture of anti-androgenic phthalates http://ntp.niehs.nih.gov/go/ts-10188-J
Diethyl phthalate 84-66-2	NIEHS 2005	Widespread consumer exposure Tests in experimental animals reveal endocrine-disrupting properties related to reproductive development • Reproductive toxicity • Multi-generation oral reproductive and developmental toxicity studies • Toxicokinetic studies (oral and dermal routes)	No Testing http://ntp.niehs.nih.gov/go/ts-10112-F
1-(Dimethylamino)-2-propanol (Dimepranol) 108-16-7	NCI 2004	Suspected of causing ocular toxicity • Genotoxicity	Selected http://ntp.niehs.nih.gov/go/ts-M040028
1,2-Dimethoxy-4-(3-fluoro-2-propenyl)benzene 161436-20-0	USDA 2008	A fluorine analog of methyl eugenol, 1,2-dimethoxy-4-(3-fluoro-2-propenyl) benzene in short field tests was as an effective attractant as methyl eugenol The incorporation of a fluorine atom in the methyl eugenol molecule profoundly slowed the metabolism in the oriental fruit fly, and had lower toxicity and lower recombinagenicity in the yeast deletion assay than methyl eugenol • Test for potential toxicity/carcinogenicity	In review/pending
Dimethylamine borane 74-94-2	NIOSH 2007	Possible contact sensitizer but insufficient evidence as determined by NIOSH Dermal Subject Matter Expert Workgroup • Dermal absorption • Skin sensitization (LLNA) • Initial toxicological characterization	Selected http://ntp.niehs.nih.gov/go/ts-M070051

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
3-Dimethylaminopropylamine 109-55-7	NCI 2005	Significant and increasing use in personal care products Widespread industrial use Lack of information on chronic toxicity Evidence of toxicity in exposed workers • Genetic toxicology, chemical disposition	Selected http://ntp.niehs.nih.gov/go/ts-11295-W
Dimorpholinodiethyl ether 6425-39-4	NCI 2006	Used in the manufacture of certain foams and adhesives Exposure through vapors and odors May help to form carcinogen nitrosomorpholine No information on toxicity of chemical found in available literature Concern that this compound could react with nitrites such as those present in the mouth to form a potent carcinogen, nitrosomorpholine • Limited testing, specialized tests, carcinogenicity	Selected http://ntp.niehs.nih.gov/go/ts-M060065
2',2'-Dithiobisbenzanilide 135-57-9	NCI 2006	Current literature on toxicological effects is inadequate Acute studies reporting irritation and sensitization data exist, but no subchronic, chronic, or genotoxicity tests were found Toxic to aquatic organisms and its release from industrial waste streams may be hazardous to the environment • Toxicity/carcinogenicity • Genotoxicity studies • Metabolism studies	Selected http://ntp.niehs.nih.gov/go/ts-M060048
Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract (299184-76-2))	Private individual 2008	Widespread use as a dietary supplement Suspicion of toxicity based on estrogenic activity and chemical structure Lack of adequate toxicity data • Comprehensive toxicological characterization	Selected 3-Butylideneephthalide (551-08-6) Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract (299184-76-2)) Ferulic acid (1135-24-6) Ligustilide (4431-01-0)
Dong quai <i>Angelica sinensis</i> root 308068-61-3	Private individual 2008		Selected — see Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract (299184-76-2))
Dong quai <i>Angelica sinensis</i> root extract 299184-76-2	Private individual 2008		Selected — see Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract (299184-76-2))
Double Fudge Concentrate	FDA 2005		Selected — see Permanent makeup inks http://ntp.niehs.nih.gov/go/ts-M070049
Double Dark Fudge True Color Concentrate	FDA 2005		Selected — see Permanent makeup inks http://ntp.niehs.nih.gov/go/ts-M070048
Dulcoside A 64432-06-0	Private individual 2009		In review/pending — see Stevia and components
Environment/copy-machine emissions and breast cancer	Private individual 2004	Requested NTP to investigate whether inhaling copy-machine fumes is a risk factor for developing breast cancer	In review/pending
2-Ethylaniline 578-54-1	NIEHS 2008		Selected — see Alkylanilines (2-Ethylaniline [578-54-1], 3-Ethylaniline [587-02-0], 3,5-Dimethylaniline [108-69-0])
3-Ethylaniline 587-02-0	NIEHS 2008		Selected — see Alkylanilines (2-Ethylaniline [578-54-1], 3-Ethylaniline [587-02-0], 3,5-Dimethylaniline [108-69-0])
Ethylene glycol 2-ethylhexyl ether 1559-35-9	NIEHS 2008	High production volume Potential worker exposures Suspicion of toxicity based on chemical structure Lack of adequate toxicity data • Reproductive toxicity studies	Selected
2-Ethylhexyl diphenyl phosphate 1241-94-7	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-10674-L
2-Ethylhexyl <i>p</i> -methoxycinnamate 5466-77-3	NCI 2006	High production volume Widespread consumer exposure as a common sunscreen active ingredient Reported estrogenic and reproductive effects • Comprehensive toxicological characterization including carcinogenicity studies	Selected http://ntp.niehs.nih.gov/go/ts-M20239

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Evening primrose oil 90028-66-3	NIEHS 2009	Use as a dietary supplement, particularly for autoimmune conditions Lack of adequate toxicological data • Initial toxicological characterization • Immunotoxicity studies	Selected
Ferulic acid 1135-24-6	Private individual 2008		Selected — see Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract [299184-76-2])
Flame retardants	CPSC 2006	Anticipated increased use in upholstered furniture and bedding and potential consumer exposures from these uses Insufficient toxicity data to assess potential health risks	Selected Antimony trioxide (1309-64-4) http://ntp.niehs.nih.gov/go/TS-10676-V <i>tert</i> -Butylphenyl diphenyl phosphate (56803-37-3) http://ntp.niehs.nih.gov/go/TS-10978-T Decabromodiphenyl oxide (1163-19-5) http://ntp.niehs.nih.gov/go/TS-10672-E 2-Ethylhexyl diphenyl phosphate (1241-94-7) http://ntp.niehs.nih.gov/go/TS-10674-L Isodecyl diphenyl phosphate (29761-21-5) http://ntp.niehs.nih.gov/go/TS-M20299 Phenol, isopropylated, phosphate (68937-41-7) http://ntp.niehs.nih.gov/go/TS-M060012 Phosphonic acid, (3-((hydroxymethyl)amino)-3-oxopropyl)-, dimethyl ester (20120-33-6) http://ntp.niehs.nih.gov/go/TS-M060010 Tricresyl phosphate (1330-78-5) http://ntp.niehs.nih.gov/go/TS-10277-D Tris(hydroxymethyl)phosphine oxide (1067-12-5) http://ntp.niehs.nih.gov/go/TS-M060011 Tris(chloropropyl)phosphate (13674-84-5) http://ntp.niehs.nih.gov/go/TS-M20263
<i>Garcinia cambogia</i> extract 90045-23-1	NCI 2005	Consumer exposure through increasing dietary supplement use Lack of adequate toxicological data • Genetic toxicology • Subchronic toxicity	Selected http://ntp.niehs.nih.gov/go/TS-M050016
Gum guggul and some of its steroidal constituents	NIEHS 2003	Consumer exposure through increasing dietary supplement use Demonstrated metabolic and hormonal effects Lack of adequate toxicological data • Toxicological characterization	Selected Guggulsterone (95975-55-6) E-Guggulsterone (39025-24-6) Z-Guggulsterone (39025-23-5) Gum guggul extract http://ntp.niehs.nih.gov/go/TS-M050066
Guggulsterone 95975-55-6	NIEHS 2003		Selected — see Gum guggul and some of its steroidal constituents
E-Guggulsterone 39025-24-6	NIEHS 2003		Selected — see Gum guggul and some of its steroidal constituents
Z-Guggulsterone 39025-23-5	NIEHS 2003		Selected — see Gum guggul and some of its steroidal constituents
Gum guggul extract	NIEHS 2003		Selected — see Gum guggul and some of its steroidal constituents
Gypsum, natural and synthetic forms	Mount Sinai Irving J. Selikoff Center for Occupational and Environmental Medicine; Operative Plasterers' and Cement Masons' International Association of the United States and Canada 2005	Widespread worker exposures in numerous occupations and to the general population after destruction of the World Trade Centers in 2001 Very limited toxicity data to assess potential health risks • Long-term toxicity studies	Deferred — additional studies are of low priority Gypsum (3397-24-5)

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Gypsum 13397-24-5	Mount Sinai Irving J. Selikoff Center for Occupational and Environmental Medicine; Operative Plasterers' and Cement Masons' International Association of the United States and Canada 2005		Deferred — see Gypsum, natural and synthetic forms
Hydroquinone 123-31-9	FDA 2009	Use in drugs and cosmetics Evidence of carcinogenicity from oral exposures in prior NTP studies Insufficient toxicological data for regulatory hazard determination • Dermal carcinogenicity studies • Reproductive toxicity studies	Selected http://ntp.niehs.nih.gov/go/ts-10022-H
Hydroxyurea 127-07-1	Private individual 2006	• Carcinogenicity studies	In review/pending http://ntp.niehs.nih.gov/go/ts-10871-K
Imidazolidinyl urea 39236-46-9	NCI 2005	Widely used preservative in personal care products Mutagenic potential Lack of adequate carcinogenicity data • Genetic toxicology • Chemical disposition via dermal absorption	Selected http://ntp.niehs.nih.gov/go/ts-M050017
Indium tin oxide 50926-11-9	NIEHS 2008	Moderate production volume Potential worker exposures Suspicion of toxicity based on chemical structure Lack of adequate toxicity data • Comprehensive toxicological characterization	Selected http://ntp.niehs.nih.gov/go/ts-M882472
Isodecyl diphenyl phosphate 29761-21-5	CPSC 2006		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-M20299
Libby amphibole, related atypical asbestos, and mineral fibers	EPA 2007	Limited data available on the adverse health effects of libby amphibole and other mineral fibers that may be present in commercial products such as insulation used in home construction, deposits mined for ores or used to produce gravel and fill • Toxicity, carcinogenicity • Mineral characterization • <i>In vitro</i> durability and toxicity studies • Subchronic and chronic toxicity/carcinogenicity studies via inhalation	Selected http://ntp.niehs.nih.gov/go/TS-M940105
Ligustilide 4431-01-0	Private individual 2008		Selected — see Dong quai (<i>Angelica sinensis</i> root [308068-61-3] and extract (299184-76-2))
α -Lipoic acid 62-46-4	NCI 2005		Deferred — see Acetyl-L-carnitine/ α -Lipoic acid supplements http://ntp.niehs.nih.gov/go/ts-M050014
2-Methoxy-4-nitroaniline 97-52-9	NCI 2006	Used in dyeing textiles, as a dye in the printing industry, and as an intermediate in the synthesis of azo dyes in tattoo inks, emulsion paints and toy enamels Given the concerns about other anisidines, findings that this agent is mutagenic when metabolically activated raises concerns about the carcinogenic potential of this compound • Chronic toxicity, developmental, reproductive • Toxicological characterization including chronic toxicity and carcinogenicity studies	Selected http://ntp.niehs.nih.gov/go/ts-M060049
L- β -Methylaminoalanine 15920-93-1	NIEHS 2008	Widespread environmental occurrence as a marine natural product Suspected risk factor for neurological disease(s) Lack of adequate toxicity data • Comprehensive toxicological characterization	Selected http://ntp.niehs.nih.gov/go/ts-08035

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Methyl iodide (Iodomethane) 74-88-4	Natural Resources Defense Council 2006	EPA is proposing to register iodomethane as replacement for methyl bromide (MB), as a pre-plant soil fumigant for peppers, strawberries and tomatoes The National Resources Defense Council believes that the safety of iodomethane cannot be fully evaluated because of gaps in the existing database The EPA evaluation of cancer risks for Methyl iodide (MI) relied on an unpublished 24 month inhalation chronic toxicity/ carcinogenicity study in rats, completed in 2005, in which over half the animals in the control and treatment groups died before the termination of the study IARC reviewed both MI and MB in 1986 and again in 1999, both times finding inadequate data to make a determination of cancer risk in humans • Carcinogenicity	In review/pending
N-Methyl-3-oxobutanamide 20306-75-6	NCI 2006	High production volume Potential worker and environmental exposures Lack of adequate toxicological data • <i>In vitro</i> and <i>in vivo</i> genotoxicity studies	Selected http://ntp.niehs.nih.gov/go/ts-M060006
Mixture of anti-androgenic phthalates	Center for the Evaluation of Risks to Human Reproduction (CERHR) 2006	Many toxicologically active phthalates appear to have a common mechanism of action Concurrent exposure of the general population to multiple phthalates may pose a greater health risk than expected based on risk estimates derived from toxicology studies on individual phthalates While the literature is rich with publications on DEHP, DBP, BBP, and other phthalates, there is clearly insufficient literature on studies involving mixtures of phthalates to support a CERHR expert panel evaluation • Reproductive toxicity • Mechanistic studies	Selected Butyl benzyl phthalate (85-68-7) http://ntp.niehs.nih.gov/go/TS-10422-E Dibutyl phthalate (84-74-2) http://ntp.niehs.nih.gov/go/TS-10987-X Di(2-ethylhexyl) phthalate (117-81-7) http://ntp.niehs.nih.gov/go/TS-10188-J
Mixtures of phthalates and other endocrine disrupting compounds (EDCs)	Private individual 2009	Humans are exposed to mixtures of these chemicals, and regulatory agencies are uncertain about methods for assessing the effects of exposure to mixtures during development These chemicals are now known interact in a dose-additive manner <i>in utero</i> , but less is known about the effects of these mixtures at lower dosage levels using robust sample sizes In addition, the end points examined to date have been limited to male reproductive toxicity, and it is now apparent that these chemicals also affect pregnancy, the female offspring and male puberty; other potential effects, such as like obesity or diabetes, also have not been studied for mixtures • Postnatal toxicological assessment following developmental exposure	In review/pending
Nanoscale materials: nanoscale gold and nanoscale silver	FDA 2007	Increasing widespread use in drug, food and cosmetic products General lack of data on the toxicology and pharmacokinetics of these materials • Nanoscale materials characterization • Metabolism and pharmacokinetic studies • Acute, subacute and subchronic toxicity studies • Examine the role of size and surface coating on the fate (ADME) and toxicity of nanoscale material in a rodent animal model	Selected Nanoscale gold (7440-57-5) Nanoscale silver (7440-22-4) http://ntp.niehs.nih.gov/go/TS-M070067
Nanoscale gold 7440-57-5	FDA 2008		Selected — see Nanoscale materials: nanoscale gold and nanoscale silver http://ntp.niehs.nih.gov/go/ts-M070067
Nanoscale silver 7440-22-4	FDA 2008		Selected — see Nanoscale materials: nanoscale gold and nanoscale silver http://ntp.niehs.nih.gov/go/ts-M070067
5,12-Naphthacenequinone 1090-13-7	Private individual 2005		In review/pending — see Polycyclic aromatic hydrocarbon quinones

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
1,2-Naphthoquinone 524-42-	Private individual 2005		In review/pending — see Phenanthraquinone (9,10-Phenanthrenequinone) and Polycyclic aromatic hydrocarbon quinones
1,4-Naphthoquinone 130-15-4	Private individual 2005		In review/pending — see Phenanthraquinone (9,10-Phenanthrenequinone) and Polycyclic aromatic hydrocarbon quinones
Naturally occurring asbestos	ATSDR/NCEH 2006	Widespread community exposure in certain geographic locales Insufficient dose-response data to characterize risk from exposure to “unregulated” asbestiform mineral fibers and naturally occurring fibrous mineral “mixtures” • Mineral characterization • <i>In vitro</i> durability and toxicity studies • Subchronic and chronic toxicity/carcinogenicity studies via inhalation	Selected http://ntp.niehs.nih.gov/go/TS-M940105
<i>N</i> -nitroso-3-methylindole 58567-91-2	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
Pentabromophenol 608-71-9	NIEHS 2004		In review/pending — see Brominated phenols http://ntp.niehs.nih.gov/go/ts-11300-K
Pentaethylenhexamine 4067-16-7	NCI 2006	Has been described as irritating, sensitizing, and corrosive in short-term tests in animals No information on the subchronic or chronic effects of exposure in humans or animals • Developmental, reproductive, short-term <i>in vitro</i> tests	No testing at this time because of the irritant and corrosive nature of this compound. http://ntp.niehs.nih.gov/go/ts-M20230
Pentafluoroiodoethane 354-64-3	NCI 2005	Being considered for many uses, including foam blowing agents, refrigeration, solvent cleaning, and aerosol propulsion These uses could lead to widespread release into the environment and to the release of iodine No subchronic or chronic testing information was found in the available literature Genotoxicity testing could help determine if additional testing is warranted • Genotoxicity	Selected http://ntp.niehs.nih.gov/go/ts-M050089
2,3-Pentanedione 600-14-6	NIEHS 2009	A diketone used as a flavoring agent in diverse food products; one of the few chemicals that imparts butter flavoring Similar diketones used in butter flavoring include diacetyl and acetoin Diacetyl has been implicated as the etiological agent in popcorn lung, a condition first observed in microwaveable popcorn factory workers; occupational exposure to diacetyl occurs by inhalation Popcorn lung is characterized by fibrotic lesions in the airways Fibrotic lesions in the airways result in a respiratory disorder called obliterative bronchiolitis Diacetyl may be removed from the butter flavoring mix used in the microwavable popcorn industry; potential flavoring substitutes include acetoin, a diacetyl trimer and 2,3-pentanedione • 14-Day acute inhalation study in rodents is proposed for initial dose range finding • After the completion of the acute study, a 90-day subchronic study is proposed with the option of conducting a chronic study pending the results of the subchronic studies	Selected http://ntp.niehs.nih.gov/go/TS-08010
Permanent makeup inks	FDA 2005	Rapidly growing practice in the United States Lack of adequate toxicological data Numerous human adverse event reports • <i>In vivo</i> allergenicity and photoallergenicity and <i>in vitro</i> phototoxicity studies	Selected Double Fudge Concentrate http://ntp.niehs.nih.gov/go/ts-M070049 Rosewood True Color Concentrate M070047 http://ntp.niehs.nih.gov/go/ts-M070047 Double Dark Fudge True Color Concentrate M070048 http://ntp.niehs.nih.gov/go/ts-M070048 Autumn Sunset True Color Concentrate M070050 http://ntp.niehs.nih.gov/go/TS-M070050

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Phenanthraquinone (9,10-Phenanthrenequinone) 130-15-4	Private individual 2005	Has been shown to have high potency for generating reactive oxygen species and recent reports also indicate other toxicologic pathways Is found in the ambient environment and appears to be formed via atmospheric chemistry It would be useful to test the two naphthoquinones as well, 1,2-naphthoquinone and 1,4-naphthoquinone Given the electrophilic activity and the potential for ROS, the quinones are worth further evaluation	In review/pending 1,2-Naphthoquinone (524-42-5) 1,4-Naphthoquinone (130-15-4) 9,10-Phenanthrenequinone (84-11-7)
9,10-Phenanthrenequinone 84-11-7	Private individual 2005		In review/pending — see Phenanthraquinone (9,10-Phenanthrenequinone) and Polycyclic aromatic hydrocarbon quinones
Phenol, isopropylated, phosphate 68937-41-7	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-M060012
Phenoxyethyl acrylate 48145-04-6	NCI 2006	High production volume Potential worker and consumer exposures Lack of adequate toxicological data	Deferred
Phosphonic acid, [3-[(hydroxymethyl)amino]-3-oxopropyl]-, dimethyl ester 20120-33-6	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/ts-M060010
<i>o</i> -Phthalaldehyde 643-79-8	NIOSH 2006	<i>o</i> -Phthalaldehyde (OPA) is marketed, sold and used as a “safe” replacement for glutaraldehyde for sterilization of heat sensitive dental and medical devices Toxicity has not been characterized, and some studies suggest that OPA may pose occupational hazards, similar to those of glutaraldehyde Data are needed to define and document the potential hazard to health-care workers handling OPA, so that appropriate guidelines and protections can be put into place • Toxicological characterization including studies to assess dermal irritation, dermal toxicity, and sensitization and asthmagenic potential	Selected http://ntp.niehs.nih.gov/go/ts-M070036
Polycyclic aromatic hydrocarbon quinones	NIEHS 2008	Nomination of phenanthraquinone by private individual in 2005 expanded to include additional compounds in this class Released into the environment from incomplete combustion of organic materials including wood and fossil fuels High potency for generating reactive oxygen species Possible role in inflammatory diseases • Initial toxicological characterization	In review/pending Acenaphthenequinone (82-86-0) 7,12-Benzanthraquinone (2498-66-0) 5,12-Naphthacenequinone (1090-13-7) 1,2-Naphthoquinone (524-42-5) 1,4-Naphthoquinone (130-15-4) 9,10-Phenanthrenequinone (84-11-7)
2-Propenamide, <i>N</i> -[3-(dimethylamino)propyl]-2-methyl- 5205-93-6	NCI 2006	High production volume Potential worker and consumer exposures Lack of adequate toxicological data Demonstrated toxicity in short-term studies • Subchronic toxicity, metabolism and disposition and genotoxicity	Selected http://ntp.niehs.nih.gov/go/ts-M060003
Rebaudioside A 58543-16-1	Private individual 2009		In review/pending — see Stevia and components
Rebaudioside C 63550-99-2	Private individual 2009		In review/pending — see Stevia and components
Ricin 9009-86-3	Private individual 2005	Concern over potential exposure to ricin	In review/pending
Rosewood True Color Concentrate	FDA 2005		Selected — see Permanent makeup inks http://ntp.niehs.nih.gov/go/ts-M070047
Saw palmetto extract 84604-15-9	Private individual 2004		In review/pending — see Creatine, Bitter orange and Saw palmetto
Silica, crystalline—quartz 14808-60-7	Private individual 2006		Selected — see Silica flour: fine and ultrafine crystalline silica particulate http://ntp.niehs.nih.gov/go/ts-M920041

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Silica flour: fine and ultrafine crystalline silica particulate	Private individual 2006	Used in skin care and pharmaceutical products Inhalation exposures associated with autoimmune disease Lack of toxicity data for oral and dermal exposures • Initial toxicological characterization via oral and dermal routes of administration • Immunotoxicity studies	Selected Silica, crystalline — quartz (14808-60-7) http://ntp.niehs.nih.gov/go/TS-M920041
Sodium benzoate and benzoic acid in Foray 48B insecticide	Private individual 2005	The nominator expressed concern regarding health hazards resulting from the aerial spraying of Foray 48B insecticide, which contains sodium benzoate and benzoic acid People who are already allergic or sensitized to these chemicals may, through being exposed via inhalation, develop serious diseases such as leukemia • Inhalation carcinogenicity	No testing Benzoic acid (65-85-0) http://ntp.niehs.nih.gov/go/TS-65850 Sodium benzoate (532-32-1)
Sodium benzoate 532-32-1	Private individual 2005		No testing — see Sodium benzoate and benzoic acid in Foray 48B insecticide
Sodium naphthenate 61790-13-4	NIEHS 2005	High production volume chemical that is considered an environmental pollutant Two-year study data are lacking • Toxicological characterization	In review/pending http://ntp.niehs.nih.gov/go/ts-M90021
Sodium orthovanadate 13721-39-6	NIEHS; EPA 2008		Selected — see Tetravalent and pentavalent vanadium compounds http://ntp.niehs.nih.gov/go/ts-08006
Sodium metavanadate 13718-26-8	NIEHS; EPA 2008		Selected — see Tetravalent and pentavalent vanadium compounds http://ntp.niehs.nih.gov/go/ts-M940043
Stevia and components	Private individual 2009	Sugar alternative Concern for any possible adverse effects on fetus	In review/pending Dulcoside A (64432-06-0) Rebaudioside A (58543-16-1) Rebaudioside C (63550-99-2) Stevia (2332-31-5) Stevia rebaudiana extract or powder (91722-21-3) Steviol (471-80-7) Stevioside (57817-89-7)
Stevia 92332-31-5	Private individual 2009		In review/pending — see Stevia and components
Stevia (<i>S. rebaudiana</i>) extract or powder 91722-21-3	Private individual 2009		In review/pending — see Stevia and components
Steviol 471-80-7	Private individual 2009		In review/pending — see Stevia and components
Stevioside 57817-89-7	Private individual 2009		In review/pending — see Stevia and components
Testosterone	Private individual 2004	The rapidly growing use of testosterone therapy has outpaced the meager scientific evidence about its benefits and risks Testosterone therapy has been approved by the FDA only for treating a narrow group of clinical conditions marked by very low testosterone levels, yet doctors have been prescribing it much more widely Last year more than 800,000 patients, mostly middle-aged men, were treated with testosterone; more studies are needed to determine the risks, such as prostate cancer and cardiovascular disease, associated with its use	In review/pending Testosterone (58-22-0) Testosterone propionate (57-85-2) Testosterone oenanthate (315-37-7)
Testosterone 58-22-0	Private individual 2004		In review/pending — see Testosterone
Testosterone propionate 57-85-2	Private individual 2004		In review/pending — see Testosterone
Testosterone oenanthate 315-37-7	Private individual 2004		In review/pending — see Testosterone

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Tetravalent and pentavalent vanadium compounds	NIEHS; EPA 2008	Widespread occurrence as drinking water contaminant and use as a dietary supplement EPA Drinking Water Contaminant Candidate List research need Pentavalent form carcinogenic via inhalation route Inadequate data to assess risk of oral exposures <ul style="list-style-type: none"> Comprehensive toxicological characterization Chronic toxicity and carcinogenicity studies via oral route Multi-generation reproductive toxicity studies 	Selected Ammonium metavanadate (7803-55-6) http://ntp.niehs.nih.gov/go/TS-08005 Sodium orthovanadate (13721-39-6) http://ntp.niehs.nih.gov/go/TS-08006 Sodium metavanadate (13718-26-8) http://ntp.niehs.nih.gov/go/TS-M940043 Vanadium pentoxide (1314-62-1) http://ntp.niehs.nih.gov/go/TS-10306-Y Vanadyl sulfate (27774-13-6) http://ntp.niehs.nih.gov/go/TS-08004
2,3,4,6-Tetrabromophenol 14400-94-3	NIEHS 2004		In review/pending — see Brominated phenols
1,1,1-Trichloroethane 71-55-6	Private individual 2004	Widely used in industry Extensive exposure to humans Incomplete knowledge of its carcinogenicity Structural similarity to known carcinogens <ul style="list-style-type: none"> Carcinogenicity 	In review/pending http://ntp.niehs.nih.gov/go/TS-10390-W
1,1,1-Trichloropropanone 918-00-3	Private individual 2009		In review/pending — see DBPs — New and Emerging Chemical Classes
Triclosan 3380-34-5	FDA 2008	Widespread use in consumer products Frequent and long-term exposure for all age groups Lack of adequate toxicity data for dermal exposures <ul style="list-style-type: none"> Carcinogenicity studies via dermal administration Phototoxicity studies 	In review/pending
Tricresyl phosphate 1330-78-5	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/TS-10277-D
4,7,10-Trioxatridecane-1,13-diamine (TTD) 4246-51-9	NCI 2006	Very little information available on toxicity; information suggests that it is severely acutely toxic TSCA 8(e) submission describes TTD as corrosive to rabbit skin and as MSDS cautions that inhalation may result in spasm, inflammation and edema of the larynx and bronchi, pneumonitis and pulmonary edema <ul style="list-style-type: none"> Limited testing, genotoxicity ICCVAM recommended <i>in vitro</i> toxicity studies Genotoxicity studies 	Selected The proposed NTP program would include TTD in the NTP high throughput screening initiative and <i>in vitro</i> genotoxicity studies Sufficient information was available on several endpoints that could be evaluated in alternative test systems for acute toxicity, corrosivity, and ocular toxicity No <i>in vivo</i> studies were proposed because its irritancy and corrosivity would likely preclude conducting humane <i>in vivo</i> toxicity studies by a relevant route of exposure at sufficiently challenging doses, although studies might be feasible at lower exposure levels http://ntp.niehs.nih.gov/go/TS-M060064
Triphenyl phosphate 115-86-6	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/TS-11042-J
Tris(hydroxymethyl)phosphine oxide 1067-12-5	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/TS-M060011
Tris(4-chlorophenyl)methane (27575-78-6) and Tris(4-chlorophenyl)methanol (3010-80-8)	NIEHS 2008	Widespread occurrence and persistence in the environment Suspicion of toxicity based on anti-androgenic activity Lack of adequate toxicity data <ul style="list-style-type: none"> Initial toxicological characterization 	Selected Tris(4-chlorophenyl)methane (27575-78-6) Tris(4-chlorophenyl)methanol (3010-80-8)
Tris(chloropropyl) phosphate, mixture 13674-84-5	CPSC 2005		Selected — see Flame retardants http://ntp.niehs.nih.gov/go/TS-M20263
Usnic acid and <i>Usnea barbata</i> herb	FDA 2005	Widely used in dietary supplement and personal care products Lack of adequate toxicological data Numerous human adverse event reports <ul style="list-style-type: none"> Toxicological characterization Genetic toxicity Developmental toxicity Reproductive toxicity Pharmacokinetic studies 	Selected Usnic acid [(+)-usnic acid] (125-46-2) http://ntp.niehs.nih.gov/go/TS-M050042 (+)-Usnic Acid (7562-61-0) http://ntp.niehs.nih.gov/go/TS-09009 Usnea lichen http://ntp.niehs.nih.gov/go/TS-09063
Usnic acid [(+)-usnic acid] 125-46-2	FDA 2005		Selected — see Usnic acid and <i>Usnea barbata</i> herb http://ntp.niehs.nih.gov/go/TS-M050042

Chemical Name & CAS Number	Nomination Source & Year	Rationale for Request & Recommended Action	Current NTP Status
Valdecoxib 181695-72-7	Private individual 2005		In review/pending — see Celebrex and Bextra
Valerian (<i>Valeriana officinalis</i>) root extracts and oil	NIEHS 2009	Use as a dietary supplement Lack of toxicological data Concern for adverse developmental and reproductive effects • Comprehensive toxicological characterization	Selected Valerian (<i>Valeriana officinalis</i>) root extract (8057-49-6) Valerian (<i>Valeriana officinalis</i>) root oil (8008-88-6) http://ntp.niehs.nih.gov/go/TS-M040029
Valerian (<i>Valeriana officinalis</i>) root extract 8057-49-6	NIEHS 2009		Selected — see Valerian (<i>Valeriana officinalis</i>) root extracts and oil
Valerian (<i>Valeriana officinalis</i>) root oil 8008-88-6	NIEHS 2009		Selected — see Valerian (<i>Valeriana officinalis</i>) root extracts and oil http://ntp.niehs.nih.gov/go/TS-M040029
Vanadium pentoxide 1314-62-1	NIEHS; EPA 2008		Selected — see Tetravalent and pentavalent vanadium compounds http://ntp.niehs.nih.gov/go/TS-10306-Y
Vanadyl sulfate 27774-13-6	NIEHS; EPA 2008		Selected — see Tetravalent and pentavalent vanadium compounds http://ntp.niehs.nih.gov/go/TS-08004
Water disinfection by-products (sodium bromate) 7789-38-0	Private individual 2009	Known occurrence in finished (ozonated) drinking water Renal carcinogen in male rats Insufficient data on carcinogenic dose-response, toxicokinetics and mode of action across species, strain, and sex • Carcinogenicity studies	In review/pending http://ntp.niehs.nih.gov/go/TS-M050035
3,5-Xylidine 108-69-0	NIEHS 2008		Selected — see Alkylanilines (2-Ethylaniline [578-54-1], 3-Ethylaniline [587-02-0], 3,5-Dimethylaniline [108-69-0]) http://ntp.niehs.nih.gov/go/TS-11430-P
Zinc 7440-66-6	ATSDR 2004	Carcinogenicity testing via oral exposure is "Priority Data Need" identified by the ATSDR	Selected — Zinc carbonate is the form of zinc to be tested Zinc carbonate, basic (5263-02-5) http://ntp.niehs.nih.gov/go/TS-M070002
Zinc carbonate, basic 5263-02-5	ATSDR 2004		Selected — see Zinc http://ntp.niehs.nih.gov/go/TS-M070002

Appendix F: Substance Names and Common Synonyms

A

2-AAF *see* 2-Acetylaminofluorene
ABP *see* 4-Aminobiphenyl
ADBAQ *see* 1-Amino-2,4-dibromoanthraquinone
AFB1 *see* Aflatoxins
2-acetamidofluorene *see* 2-Acetylaminofluorene
2-acetaminofluorene *see* 2-Acetylaminofluorene
acetate blue G *see* Disperse Blue 1
acetic aldehyde *see* Acetaldehyde
acetothioamide *see* Thioacetamide
acetylaldehyde *see* Acetaldehyde
acetylhydride *see* Acetaldehyde
acid red 114 (C.I.) *see* 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine, Dyes Metabolized to 3,3'-Dimethylbenzidine
acrylic acid amide *see* Acrylamide
actinolite *see* Asbestos
alcohol drinking *see* Alcoholic Beverage Consumption
aluminum-beryllium alloy *see* Beryllium and Beryllium Compounds
2-amino-9,10-anthracenedione *see* 2-Aminoanthraquinone
2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline *see* Heterocyclic Amines (Selected)
2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline *see* Heterocyclic Amines (Selected)
1-amino-2-methyl-9,10-anthracenedione *see* 1-Amino-2-methylanthraquinone
2-amino-3-methyl-3*H*-imidazo(4,5-*f*)quinoline *see* Heterocyclic Amines (Selected), 2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ)
2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine *see* Heterocyclic Amines (Selected)
2-amino-3-methylimidazo[4,5-*f*]quinoline *see* Heterocyclic Amines (Selected)
4-amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1*H*)-one *see* Azacitidine
3-amino-1,2,4-triazol *see* Amitrole
2-aminoanisole hydrochloride *see* *o*-Anisidine and Its Hydrochloride
2-aminoazotoluene *see* *o*-Aminoazotoluene
4-aminodiphenyl *see* 4-Aminobiphenyl
4-[(4-aminophenyl)(4-imino-2,5-cyclohexadien-1-ylidene)methyl]-benzenamine, monohydrochloride *see* Basic Red 9 Monohydrate
aminotriazole *see* Amitrole
amosite *see* Asbestos
analgesic mixtures containing phenacetin *see* Phenacetin and Analgesic Mixtures Containing Phenacetin
2-anisidine hydrochloride *see* *o*-Anisidine and Its Hydrochloride
anthophyllite *see* Asbestos
Aroclor 1254 *see* Polychlorinated Biphenyls
Aroclor 1260 *see* Polychlorinated Biphenyls
5-AzaC *see* Azacitidine
5-azacytidine *see* Azacitidine

B

BBMP *see* 2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)

BCME *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
BCNU *see* Nitrosourea Chemotherapeutic Agents, Bis(chloroethyl) Nitrosourea
BHA *see* Butylated Hydroxyanisole
basic fuchsin *see* Basic Red 9 Monohydrate
basic red 9 *see* Basic Red 9 Monohydrate
basic red 9 monohydrochloride (C.I.) *see* Basic Red 9 Monohydrate
beer *see* Alcoholic Beverage Consumption
benz[*a*]anthracene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
benz[*a*]anthracene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Benz[*a*]anthracene
benz[*e*]acephenanthrylene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Benzo[*b*]fluoranthene
1,2-benzanthracene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Benz[*a*]anthracene
benzidine dye class *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine
benzo[*a*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
benzo[*b*]fluoranthene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
benzo[*j*]fluoranthene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
benzo[*k*]fluoranthene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
benzo[*rst*]pentaphene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,i*]pyrene
benzol *see* Benzene
beryl ore *see* Beryllium and Beryllium Compounds
beta-aminoanthraquinone *see* 2-Aminoanthraquinone
beta-naphthylamine *see* 2-Naphthylamine
bidis *see* Tobacco-Related Exposures, Tobacco Smoking
2,2'-bioxirane *see* Diepoxybutane
4-biphenylamine *see* 4-Aminobiphenyl
2,2-bis(bromomethyl)propane-1,3-diol *see* 2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)
4-[bis(2-chloroethyl)amino]-L-phenylalanine *see* Melphalan
bis(2-chloroethyl)sulfide *see* Mustard Gas
4-[bis(2-chloromethyl)amino]benzenebutanoic acid *see* Chlorambucil
4,4'-bis(dimethylamino)benzophenone *see* Michler's Ketone
bis(2-ethylhexyl) ester 1,2-benzenedicarboxylic acid *see* Di(2-ethylhexyl) Phthalate
bis(2-ethylhexyl phthalate) *see* Di(2-ethylhexyl) Phthalate
3,3-bis(4-hydroxyphenyl)-1-(3*H*)-isobenzofuranone *see* Phenolphthalein
bischloroethyl nitrosourea *see* Nitrosourea Chemotherapeutic Agents, Bis(chloroethyl) Nitrosourea
broad-spectrum ultraviolet radiation *see* Ultraviolet Radiation Related Exposures
bromoethene *see* Vinyl Halides (Selected), Vinyl Bromide
busulfan *see* 1,4-Butanediol Dimethanesulfonate
1,3-butadiene diepoxide *see* Diepoxybutane
1,4-butanediol dimethanesulphonate *see* 1,4-Butanediol Dimethanesulfonate
butter yellow *see* *o*-Aminoazotoluene

C

C.I. acid red 114 *see* 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine

C.I. direct black 38 *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

C.I. disperse blue 1 *see* Disperse Blue 1

C.I. direct blue 6 *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

C.I. direct blue 15 *see* 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine

C.I. direct brown 95 *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

C.I. disperse orange *see* 1-Amino-2-methylantraquinone

C.I. solvent yellow 3 *see* *o*-Aminoazotoluene

CCNU *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea

CMME *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

calcium arsenate *see* Arsenic and Inorganic Arsenic Compounds

calcium arsenite *see* Arsenic and Inorganic Arsenic Compounds

calcium chromate *see* Chromium Hexavalent Compounds

camphechlor *see* Toxaphene

carbamodithioic acid, diethyl-, 2-chloro-2-propenyl ester *see* Sulfallate

carmustine *see* Nitrosourea Chemotherapeutic Agents, Bis(chloroethyl) Nitrosourea

cemented carbides *see* Cobalt-Tungsten Carbide: Powders and Hard Metals

chewing tobacco *see* Tobacco-Related Exposures, Smokeless Tobacco

chinosfer *see* Iron Dextran Complex

2-chlorallyl diethyldithiocarbamate *see* Sulfallate

chlordecone *see* Kepone

chlorethamine *see* Nitrogen Mustard Hydrochloride

chlorinated camphene *see* Toxaphene

4-chloro-1,2-benzenediamine *see* 4-Chloro-*o*-phenylenediamine

2-chloro-1,3-butadiene *see* Chloroprene

1-chloro-2,3-dibromopropane *see* 1,2-Dibromo-3-chloropropane

3-chloro-1,2-dibromopropane *see* 1,2-Dibromo-3-chloropropane

1-chloro-2-methyl-1-propene *see* Dimethylvinyl Chloride

3-chloro-2-methyl-1-propene *see* 3-Chloro-2-methylpropene

4-chloro-2-methylaniline *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride

4-chloro-2-methylbenzenamine *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride

4-chloro-2-methylbenzenamine hydrochloride *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride

1-chloro-2-methylpropene *see* Dimethylvinyl Chloride

2-chloro-*N*-(2-chloroethyl)-*N*-methylethanamine *see* Nitrogen Mustard Hydrochloride

4-chloro-*o*-toluidine *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride

4-chloro-*o*-toluidine hydrochloride *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride

4-chloro-1,2-phenylenediamine *see* 4-Chloro-*o*-phenylenediamine

chlorocamphene *see* Toxaphene

chloroethene *see* Vinyl Halides (Selected), Vinyl Chloride

2-(((2-chloroethyl)nitrosoamino)carbonyl)amino)-2-deoxy-D-glucose *see* Nitrosourea Chemotherapeutic Agents, Chlorozotocin

chloromethyl methyl ether *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

chloromethyl oxirane *see* Epichlorohydrin

chromated copper arsenate (CCA) *see* Arsenic and Inorganic Arsenic Compounds *and* Chromium Hexavalent Compounds

chromium VI *see* Chromium Hexavalent Compounds

chrysazin *see* Danthron

chrysotile *see* Asbestos

ciclosporin *see* Cyclosporin A

cigarettes *see* Tobacco-Related Exposures, Tobacco Smoking

cigars *see* Tobacco-Related Exposures, Tobacco Smoking

cis-dichlorodiamine platinum (II) *see* Cisplatin

cobaltous sulfate *see* Cobalt Sulfate

conjugated estrogens *see* Estrogens, Steroidal

copper-beryllium alloy *see* Beryllium and Beryllium Compounds

crystalite *see* Silica, Crystalline (Respirable Size)

crocidolite *see* Asbestos

crystalline silica, respirable *see* Silica, Crystalline (Respirable Size)

(*R*-(*R,*R**-(*E*)))**-cyclic(L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl-3-hydroxy-*N*,4-dimethyl-L-2-amino-6-octenoyl-L- α -aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl) *see* Cyclosporin A

cyclosporine *see* Cyclosporin A

D

DAAB *see* Diazoaminobenzene

DBP *see* 2,3-Dibromo-1-propanol

DDT *see* Dichlorodiphenyltrichloroethane

DEHP *see* Di(2-ethylhexyl) Phthalate

DEN *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodiethylamine

DES *see* Diethylstilbestrol

DMN *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodimethylamine

dantrol *see* Danthron

decabromobiphenyl *see* Polybrominated Biphenyls

1,1a,3,3a,4,5,5a,5b,6-decachlorooctahydro-1,3,4-metheno-2H-cyclobuta[*cd*]pentalen-2-one *see* Kepone

2-deoxy-2{[methyl-nitrosoamino]carbonyl}amino}-D-glucopyranose *see* Nitrosourea Chemotherapeutic Agents, Streptozotocin

dextran iron complex *see* Iron Dextran Complex

4,4'-diaminodiphenyl ether *see* 4,4'-Oxydianiline

diaminodiphenyl ether *see* 4,4'-Oxydianiline

4,4'-diaminodiphenyl sulfide *see* 4,4'-Thiodianiline

4,4'-diaminodiphenylmethane *see* 4,4'-Methylenedianiline and Its Dihydrochloride

dibenz[*a,h*]acridine *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenz[*a,j*]acridine *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenz[*a,h*]anthracene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenzo[*b,c,e,f*]chrysene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,h*]pyrene

dibenzo[*def,p*]chrysene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,l*]pyrene

dibenzo[*a,e*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenzo[*a,h*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenzo[*a,i*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

dibenzo[*a,l*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

7H-dibenzo[*c,g*]carbazole *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

1,2,4,5-dibenzopyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,e*]pyrene

3,4,9,10-dibenzopyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,i*]pyrene

2,4-dibromo-1-anthraquinonylamine *see* 1-Amino-2,4-dibromoanthraquinone

2,3-dibromo-1-propanol phosphate (3:1) *see* Tris(2,3-dibromopropyl) Phosphate

dibromoneopentyl glycol *see* 2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)

2,3-dibromopropan-1-ol *see* 2,3-Dibromo-1-propanol

2,3-dibromopropanol *see* 2,3-Dibromo-1-propanol

3,3'-dichloro-(1,1'-biphenyl)-4,4'-diamine *see* 3,3'-Dichlorobenzidine Its Dihydrochloride

3,3'-dichloro-(1,1'-biphenyl)-4,4'-diamine dihydrochloride *see* 3,3'-Dichlorobenzidine and Its Dihydrochloride

2,4-dichloro-1-(4-nitrophenoxy)benzene *see* Nitrofen

1,3-dichloro-1-propene *see* 1,3-Dichloropropene (Technical Grade)

2,2-dichloro-*N*-(2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl)-, (R-(R*,R*))-(nitrophenyl)ethyl)acetamide *see* Chloramphenicol

[R-(R*,R*)]-2,2-dichloro-*N*-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl)acetamide *see* Chloramphenicol

dichlorobromomethane *see* Bromodichloromethane

dichlorodimethyl ether, symmetrical *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether

2,4-dichlorophenyl-*p*-nitrophenyl ether *see* Nitrofen

diethyl ester sulfuric acid *see* Diethyl Sulfate

(E)-4,4'-(1,2-diethyl-1,2-ethenediyl)bisphenol *see* Diethylstilbestrol

diethyl sulphate *see* Diethyl Sulfate

diethylnitrosamine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodiethylamine

2,3-dihydro-6-propyl-2-thioxo-4(1*H*)-pyrimidinone *see* Propylthiouracil

1,8-dihydroxy-9,10-anthracenedione *see* Danthron

1,8-dihydroxyanthraquinone *see* Danthron

1,3-diisocyanatomethylbenzene *see* Toluene Diisocyanates

Dilantin *see* Phenytoin and Phenytoin Sodium

3,3'-dimethoxybenzidine dye class *see* 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine

dimethyl ester sulfuric acid *see* Dimethyl Sulfate

3,4-dimethyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine *see* Heterocyclic Amines (Selected), 2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline (MeIQ)

3,8-dimethyl-3*H*-imidazo[4,5-*f*]quinoxalin-2-amine *see* Heterocyclic Amines (Selected), 2-Amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline (MeIQx)

5-(3,3-dimethyl-1-triazenyl)1*H*-imidazole-4-carboxamide *see* Dacarbazine

4,4'-(dimethylamino)benzophenone *see* Michler's Ketone

3,3'-dimethylbenzidine dye class *see* 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine, Dyes Metabolized to 3,3'-Dimethylbenzidine

dimethylcarbamic chloride *see* Dimethylcarbamoyl Chloride

(1,1-dimethylethyl)-4-methoxyphenol *see* Butylated Hydroxyanisole

dimethylnitrosamine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodimethylamine

1,6-dinitropyrene *see* Nitroarenes (Selected)

1,8-dinitropyrene *see* Nitroarenes (Selected)

dioctyl phthalate *see* Di(2-ethylhexyl) Phthalate

dioxin *see* 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

(Z)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N,N*-dimethylethanamine *see* Tamoxifen

5,5-diphenyl-2,4-imidazolidinedione *see* Phenytoin and Phenytoin Sodium

diphenylan *see* Phenytoin and Phenytoin Sodium

diphenylhydantoin *see* Phenytoin and Phenytoin Sodium

5,5-diphenylhydantoin *see* Phenytoin and Phenytoin Sodium

1,2-diphenylhydrazine *see* Hydrazobenzene

1,3-diphenyltriazene *see* Diazoaminobenzene

direct black 38 (C.I.) *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

direct blue 6 (C.I.) *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

direct blue 15 (C.I.) *see* 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine

direct brown 95 (C.I.) *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

di-*sec*-octyl phthalate *see* Di(2-ethylhexyl) Phthalate

disodium hydrogen arsenate *see* Arsenic and Inorganic Arsenic Compounds

disperse orange *see* 1-Amino-2-methylantraquinone

1,1a,2,2,3,3a,4,5,5,5a,5b,6-dodecachlorooctahydro-1,3,4-metheno-1*H*-cyclobuta(*cd*)pentalene *see* Mirex

doxorubicin hydrochloride *see* Adriamycin

dyes metabolized to benzidine *see* Benzidine and Dyes Metabolized to Benzidine, Dyes Metabolized to Benzidine

dyes metabolized to 3,3'-dimethoxybenzidine *see* 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine

dyes metabolized to 3,3'-dimethylbenzidine *see* 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine, Dyes Metabolized to 3,3'-Dimethylbenzidine

E

EDB *see* 1,2-Dibromoethane

ENU *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-ethylurea

ETS *see* Tobacco-Related Exposures, Environmental Tobacco Smoke

ETU *see* Ethylene Thiourea

environmental tobacco smoke *see* Tobacco-Related Exposures

1,2-epoxyethylbenzene *see* Styrene-7,8-oxide

estradiol *see* Estrogens, Steroidal

estrone *see* Estrogens, Steroidal

ethanal *see* Acetaldehyde

ethanol *see* Alcoholic Beverage Consumption

ethinylestradiol *see* Estrogens, Steroidal

ethyl aldehyde *see* Acetaldehyde
ethyl carbamate *see* Urethane
ethyl methanesulphonate *see* Ethylmethanesulfonate
1-ethyl-1-nitrosourea *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-ethylurea
ethylene dibromide *see* 1,2-Dibromoethane
ethylene dichloride *see* 1,2-Dichloroethane
ethylenethiourea *see* Ethylene Thiourea
eugenol methyl ether *see* Methyleugenol

F

FF-1 *see* Polybrominated Biphenyls
ferrochromium *see* Chromium Hexavalent Compounds
FireMaster FF1 *see* Polybrominated Biphenyls
Firemaster t 23 *see* Tris(2,3-dibromopropyl) Phosphate
flavatoxin *see* Aflatoxins
2-fluorenylacetylacetamide *see* 2-Acetylaminofluorene
fluoroethene *see* Vinyl Halides (Selected), Vinyl fluoride
formalin *see* Formaldehyde

G

gamma radiation *see* Ionizing Radiation, X-Radiation and Gamma Radiation
glycidaldehyde *see* Glycidol

H

HBV *see* Hepatitis B Virus
HCH *see* Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
HCV *see* Hepatitis C Virus
HPV *see* Human Papillomaviruses: Some Genital-Mucosal Types
hard metals *see* Cobalt-Tungsten Carbide: Powders and Hard Metals
hexabromobiphenyl *see* Polybrominated Biphenyls
1,4,5,6,7,7-hexa-chlorobicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid *see* Chlorendic Acid
hexachlorocyclohexane *see* Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
hexachlorocyclohexane isomers *see* Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
hexamethylphosphoric triamide *see* Hexamethylphosphoramide
hexavalent chromium compounds *see* Chromium Hexavalent Compounds
17-hydroxy-2-(hydroxymethylene)-17-methyl-5 α ,17 β -androstane-3-one *see* Oxymetholone
(17 α)-17-hydroxy-19-norpregn-4-en-20-yn-3-one *see* Norethisterone
14-hydroxydaunomycin *see* Adriamycin

I

IQ *see* Heterocyclic Amines (Selected), 2-Amino-3-methylimidazo[4,5-*f*]quinoline
2-imidazolidinethione *see* Ethylene Thiourea
indeno[1,2,3-*cd*]pyrene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
inorganic acid mists *see* Strong Inorganic Acid Mists Containing Sulfuric Acid
insulation glass fibers *see* Certain Glass Wool Fibers (Inhalable)

involuntary smoking *see* Tobacco-Related exposure, Environmental Tobacco Smoke

iron-carbohydrate complexes *see* Iron Dextran Complex

K

Kanechlor 500 *see* Polychlorinated Biphenyls

L

lead acetate *see* Lead and Lead Compounds
lead arsenate *see* Arsenic and Inorganic Arsenic Compounds
lead chromates *see* Chromium Hexavalent Compounds and Lead and Lead Compounds
lead phosphate *see* Lead and Lead Compounds
lomustine *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea
L-phenylalanine, N-[(5-chloro-3,4-dihydro-8-hydroxy-3-methyl-1-oxo-1*H*-2-benzopyran-7-yl)-carbonyl]-, (R)- *see* Ochratoxin A
lubricant base oils *see* Mineral Oils: Untreated and Mildly Treated

M

MBOCA *see* 4,4'-Methylenebis(2-chloroaniline)
MeCCNU *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea
MeIQ *see* Heterocyclic Amines (Selected), 2-Amino-3,4-dimethylimidazo[4,5-*f*]quinoline
MeIQx *see* Heterocyclic Amines (Selected), 2-Amino-3,8-dimethylimidazo-[4,5-*f*]quinoxaline
MMNG *see* *N*-Nitrosamines: 15 Listings, *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine
MOCA *see* 4,4'-Methylenebis(2-chloroaniline)
MVNA *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosomethylvinylamine
man-made mineral fibers *see* Ceramic Fibers (Respirable Size) and Certain Glass Wool Fibers (Inhalable)
mechlorethamine hydrochloride *see* Nitrogen Mustard Hydrochloride
mestranol *see* Estrogens, Steroidal
metallic arsenic *see* Arsenic and Inorganic Arsenic Compounds
metallic nickel *see* Nickel Compounds and Metallic Nickel
methallyl chloride *see* 3-Chloro-2-methylpropene
4-methoxy-1,3-benzenediamine *see* 2,4-Diaminoanisole Sulfate
9-methoxy-7*H*-furo [3,2*g*] [1] benzopyran-7-one *see* Methoxsalen with Ultraviolet A Therapy
2-methoxy-5-methylbenzenamine *see* *p*-Cresidine
1-methoxy-2-nitrobenzene *see* *o*-Nitroanisole
4-methoxy-*m*-phenylenediamine sulfate *see* 2,4-Diaminoanisole Sulfate
2-methoxybenzenamine *see* *o*-Anisidine and Its Hydrochloride
8-methoxyypsoralen *see* Methoxsalen with Ultraviolet A Therapy
4-methyl-1,3-benzenediamine *see* 2,4-Diaminotoluene
2-methyl-1,3-butadiene *see* Isoprene
methyl chloromethyl ether *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
methyl ester methanesulfonic acid *see* Methyl Methanesulfonate
methyl eugenol *see* Methyleugenol
3-methyl-3*H*-imidazo[4,5-*f*]quinolin-2-amine *see* Heterocyclic Amines (Selected), 2-Amino-3-methylimidazo[4,5-*f*]quinoline (IQ)
2-methyl-4-[(2-methylphenyl)azo]-benzenamine *see* *o*-Aminoazotoluene

6-[(1-methyl-4-nitro-1*H*-imidazol-5-yl)thio]-1*H*-purine *see* Azathioprine

2-methyl-5-nitro-1*H*-imidazole-1-ethanol *see* Metronidazole

1-methyl-6-phenyl-1*H*-imidazo[4,5-*b*]pyridin-2-amine *see* Heterocyclic Amines (Selected), 2-Amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine (PhIP)

2-methylaniline hydrochloride *see* *o*-Toluidine and *o*-Toluidine Hydrochloride

2-methylbenzenamine *see* *o*-Toluidine and Its Hydrochloride

2-methylbenzenamine hydrochloride *see* *o*-Toluidine and *o*-Toluidine Hydrochloride

methyl-CCNU *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea

5-methylchrysene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings

methylene chloride *see* Dichloromethane

4,4'-methylenebis(2-chlorobenzenamine) *see* 4,4'-Methylenebis(2-chloroaniline)

4,4'-methylenebisbenzenamine *see* 4,4'-Methylenedianiline and Its Dihydrochloride

4,4'-methylenebisbenzenamine dihydrochloride *see* 4,4'-Methylenedianiline and Its Dihydrochloride

methylenedianiline dihydrochloride *see* 4,4'-Methylenedianiline and Its Dihydrochloride

4,4'-methylenedianiline dihydrochloride *see* 4,4'-Methylenedianiline and Its Dihydrochloride

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone *see* *N*-Nitrosamines: 15 Listings, 4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone

methyloxirane *see* Propylene Oxide

Michler's base *see* 4,4'-Methylenebis(*N,N*-dimethyl)benzenamine

mildly treated mineral oils *see* Mineral Oils: Untreated and Mildly Treated

mists, strong inorganic acid *see* Strong Inorganic Acid Mists Containing Sulfuric Acid

Myleran *see* 1,4-Butanediol Dimethanesulfonate

N

***N*-butyl-*N*-nitroso-1-butamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-butylamine

***N*-(2-chloroethyl)-*N'*-cyclohexyl-*N*-nitrosourea** *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea

***N*-(2-chloroethyl)-*N*-(1-methyl-2-phenoxybenzenemethanamine hydrochloride)** *see* Phenoxybenzamine Hydrochloride

***N*-dibutylnitrosoamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-butylamine

***N*-(4-ethoxyphenyl)acetamide** *see* Phenacetin and Analgesic Mixtures Containing Phenacetin

***N*-ethyl-*N*-nitroso-ethanamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodiethylamine

***N*-ethyl-*N*-nitrosourea** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-ethylurea

***N*-methyl-*N*-nitroso-ethenylamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosomethylvinylamine

***N*-methyl-*N*-nitroso-glycine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrososarcosine

***N*-methyl-*N*-nitroso-*N'*-nitroguanidine** *see* *N*-Nitrosamines: 15 Listings, *N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine

***N*-methyl-*N*-nitrosomethanamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodimethylamine

***N*-methyl-*N*-nitrosourea** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-methylurea

***N*-(1-methylethyl)-4-[(2-methylhydrazino)methyl]-benzamide monohydrochloride** *see* Procarbazine and Its Hydrochloride

***N*-methylvinylnitrosamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosomethylvinylamine

***N,N*-bis(carboxymethyl)glycine** *see* Nitriilotriacetic Acid

***N,N'*-bis(2-chloroethyl)-*N*-nitrosourea** *see* Nitrosourea Chemotherapeutic Agents, Bis(chloroethyl) Nitrosourea

***N,N*-bis(2-chloroethyl)tetrahydro-2*H*-1,3,2-oxaphosphorin-2-amine, 2-oxide monohydrate** *see* Cyclophosphamide

***N,N*-dibutylnitrosoamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-butylamine

***N,N*-diethyldithiocarbamic acid 2-choroallyl ester** *see* Sulfallate

***N,N*-dimethyl-4-(phenylazo)-benzenamine** *see* 4-Dimethylaminoazobenzene

***N*-Nitroso-*N*-methylglycine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrososarcosine

***N*-nitroso-*N*-propyl-1-propanamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-propylamine

***N*-nitrosodipropylamine** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-propylamine

***N*-nitrosoethylurea** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-ethylurea

***N*-nitrosomethylurea** *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-methylurea

***N*-nitrosophenylhydroxylamine, ethanalamine salt** *see* Cupferron

NDEA *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodiethylamine

NEU *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-ethylurea

NMU *see* *N*-Nitrosamines: 15 Listings, *N*-Nitroso-*N*-methylurea

NNK *see* *N*-Nitrosamines: 15 Listings, 4-(*N*-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone

NNN *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrososarcosine

naphtho(1,2,3,4-*def*)chrysene *see* Polycyclic Aromatic Hydrocarbons: 15 Listings, Dibenzo[*a,e*]pyrene

neutrons *see* Ionizing Radiation

nickelocene *see* Nickel Compounds and Metallic Nickel

2-nitroanisole *see* *o*-Nitroanisole

nitrochlor *see* Nitrofen

6-nitrochrysene *see* Nitroarenes (Selected)

1-nitropyrene *see* Nitroarenes (Selected)

4-nitropyrene *see* Nitroarenes (Selected)

1-nitroso-piperidine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosopiperidine

3-(1-nitroso-2-pyrrolidinyl)pyridine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrososarcosine

nitrosodibutylamine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodi-*n*-butylamine

2,2'-(nitrosoimino)bis[ethanol] *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosodiethanolamine

4-nitrosomorpholine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosomorpholine

1-nitrosopyrrolidine *see* *N*-Nitrosamines: 15 Listings, *N*-Nitrosopyrrolidine

O

***o*-aminoanisole** *see* *o*-Anisidine and Its Hydrochloride

o-dianisidine *see* 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine, Dyes Metabolized to 3,3'-Dimethoxybenzidine
o-tolidine *see* 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine, Dyes Metabolized to 3,3'-Dimethylbenzidine
octabromobiphenyl *see* Polybrominated Biphenyls
1,2-oxathiolane, 2,2-dioxide *see* 1,3-Propane Sultone
2-oxetanone *see* β -Propiolactone
oxirane *see* Ethylene Oxide
oxiranemethanol *see* Glycidol
3-oxiranyl-7-oxabicyclo[4.1.0]heptane *see* 4-Vinyl-1-cyclohexene Diepoxide
4,4'-oxybisbenzenamine *see* 4,4'-Oxydianiline

P

p-aminobiphenyl *see* 4-Aminobiphenyl
p-aminodiphenyl *see* 4-Aminobiphenyl
p-dichlorobenzene *see* 1,4-Dichlorobenzene
p-dimethylaminoazobenzene *see* 4-Dimethylaminoazobenzene
p-roaniline hydrochloride *see* Basic Red 9 Monohydrate
p,p'-tetramethyldiaminodiphenylmethane *see* 4,4'-Methylenebis(N,N-Dimethyl)benzenamine
PAHs *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
PBBs *see* Polybrominated Biphenyls
PCBs *see* Polychlorinated Biphenyls
PCDD *see* 2,3,7,8-Tetrachlorodibenzo-p-dioxin
PhIP *see* Heterocyclic Amines (Selected), 2-Amino-1-methyl-6-phenylimidazo-[4,5-b]pyridine
PUVA *see* Methoxsalen with Ultraviolet A Therapy
paraffins, chlorinated *see* Chlorinated Paraffins
paraformaldehyde *see* Formaldehyde
perchloroethylene *see* Tetrachloroethylene
petroleum *see* Mineral Oils: Untreated and Mildly Treated
3-phenylazo-2,6-diaminopyridine hydrochloride *see* Phenazopyridine Hydrochloride
3-(phenylazo)-2,6-pyridinediamine monohydrochloride *see* Phenazopyridine Hydrochloride
2,2'-[phenylenebis(oxyethylene)]bisoxirane *see* Diglycidyl Resorcinol Ether
phenyloxirane *see* Styrene-7,8-oxide
1,1',1''-phosphinothioylidynetrisaziridine *see* Thiotepa
pipe smoking *see* Tobacco-Related Exposures
piperazine estrone sulfate *see* Estrogens, Steroidal
platinum, diamminedichloro-, (SP-4-2)- *see* Cisplatin
polychlorinated camphenes *see* Toxaphene
polychlorocamphene *see* Toxaphene
polychlorophenols *see* 2,4,6-Trichlorophenol
potassium arsenate *see* Arsenic and Inorganic Arsenic Compounds
potassium arsenite *see* Arsenic and Inorganic Arsenic Compounds
potassium chromate *see* Chromium Hexavalent Compounds
potassium dichromate *see* Chromium Hexavalent Compounds
pregn-4-ene-3,20-dione *see* Progesterone
propane sultone *see* 1,3-Propane Sultone
2-propenamide *see* Acrylamide
2-propenenitrile *see* Acrylonitrile
5-(2-propenyl)-1,3-benzodioxole *see* Safrole
6-propyl-2-thiouracil *see* Propylthiouracil

propylenimine *see* 2-Methylaziridine
psoralen *see* Methoxsalen with Ultraviolet A Therapy
pyridium *see* Phenazopyridine Hydrochloride

Q

quartz *see* Silica, Crystalline (Respirable Size)

R

radiation, ionizing *see* Ionizing Radiation
radon *see* Ionizing Radiation
refractory ceramic fibers *see* Ceramic Fibers (Respirable Size)
resorcinol diglycidyl ether *see* Diglycidyl Resorcinol Ether
respirable crystalline silica *see* Silica, Crystalline (Respirable Size)

S

sawdust *see* Wood Dust
second hand smoke *see* Tobacco-Related Exposures, Environmental Tobacco Smoke
Selsun *see* Selenium Sulfide
semustine *see* Nitrosourea Chemotherapeutic Agents, 1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea
sidestream smoke *see* Tobacco-Related Exposures, Environmental Tobacco Smoke
sintered carbides *see* Cobalt-Tungsten Carbide: Powders and Hard Metals
smokeless tobacco *see* Tobacco-Related Exposures
snuff *see* Tobacco-Related Exposures, Smokeless Tobacco
sodium arsenate *see* Arsenic and Inorganic Arsenic Compounds
sodium arsenite *see* Arsenic and Inorganic Arsenic Compounds
sodium chromate *see* Chromium Hexavalent Compounds
sodium dichromate *see* Chromium Hexavalent Compounds
sodium equilin sulfate *see* Estrogens, Steroidal
sodium estrone sulfate *see* Estrogens, Steroidal
solar radiation *see* Ultraviolet Radiation Related Exposures
solvent blue 18 *see* Disperse Blue 1
special-purpose glass fibers *see* Certain Glass Wool Fibers (Inhalable)
spirits *see* Alcoholic Beverage Consumption
steroidal estrogens *see* Estrogens, Steroidal
stilbestrol *see* Diethylstilbestrol
strontium chromate *see* Chromium Hexavalent Compounds
styrene oxide *see* Styrene-7,8-oxide
sulfur mustard *see* Mustard Gas
sulfuric acid *see* Strong Inorganic Acid Mists Containing Sulfuric Acid
sunbeds *see* Ultraviolet Radiation Related Exposures, Sunlamps or Sunbeds, Exposure to
sunlamps *see* Ultraviolet Radiation Related Exposures
synthetic mineral fibers *see* Ceramic Fibers (Respirable Size) and Certain Glass Wool Fibers (Inhalable)
synthetic vitreous fibers *see* Certain Glass Wool Fibers (Inhalable)

T

TCDD *see* 2,3,7,8-Tetrachlorodibenzo-p-dioxin
TCE *see* Trichloroethylene
TEPA *see* Thiotepa
TFE *see* Tetrafluoroethylene

Telone II *see* 1,3-Dichloropropene (Technical Grade)
1,4,5,8-tetraamino-9,10-anthracenedione *see* Disperse Blue 1
1,4,5,8-tetraaminoanthraquinone *see* Disperse Blue 1
tetrachloroethene *see* Tetrachloroethylene
tetrachloromethane *see* Carbon Tetrachloride
tetraethyl lead *see* Lead and Lead Compounds
tetrafluoroethene *see* Tetrafluoroethylene
tetramethyl lead *see* Lead and Lead Compounds
1,1'-thiobis(2-chloroethane) *see* Mustard Gas
4,4'-thiobisbenzenamine *see* 4,4'-Thiodianiline
thiodianiline *see* 4,4'-Thiodianiline
thorium dioxide *see* Ionizing Radiation
Thorotrast *see* Ionizing Radiation, Thorium Dioxide
tobacco smoking *see* Tobacco-Related Exposures
2,4-toluene diisocyanate *see* Toluene Diisocyanates
2,6-toluene diisocyanate *see* Toluene Diisocyanates
toluenediamine *see* 2,4-Diaminotoluene
tremolite *see* Asbestos
1,1,1-trichloro-2,2-bis(*p*-chlorophenyl) ethane *see* Dichlorodiphenyltrichloroethane
trichloroethene *see* Trichloroethylene
trichloromethane *see* Chloroform
***a,a,a*-trichlorotoluene** *see* Benzotrichloride
tridymite *see* Silica, Crystalline (Respirable Size)
triethylenethiophosphoramidate *see* Thiotepa
trimethylene methanesulfonate *see* 1,4-Butanediol Dimethanesulfonate
trioxane *see* Formaldehyde
tris(1-aziridinyl)phosphine sulfide *see* Thiotepa
tungsten carbides *see* Cobalt–Tungsten Carbide: Powders and Hard Metals

U

UMDH *see* 1,1-Dimethylhydrazine
UVA *see* Ultraviolet Radiation Related Exposures
UVB *see* Ultraviolet Radiation Related Exposures
UVC *see* Ultraviolet Radiation Related Exposures
UVR *see* Ultraviolet Radiation Related Exposures
untreated mineral oils *see* Mineral Oils: Untreated and Mildly Treated
urethan *see* Urethane

V

4-vinylcyclohexene diepoxide *see* 4-Vinyl-1-cyclohexene Diepoxide
vinylcyclohexene dioxide *see* 4-Vinyl-1-cyclohexene Diepoxide
vitreous fibers, synthetic *see* Certain Glass Wool Fibers (Inhalable)

W

wine *see* Alcoholic Beverage Consumption

X

xanthotoxin *see* Methoxsalen with Ultraviolet A Therapy
X-radiation *see* Ionizing Radiation
X-rays *see* Ionizing Radiation, X-Radiation and Gamma Radiation

Y

yohimban-16-carboxylic acid, 11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]-, methyl ester, (3 β ,16 β ,17 α ,18 β ,20 α)- *see* Reserpine

Z

zeolites *see* Erionite
zinc beryllium silicate *see* Beryllium and Beryllium Compounds
zinc chromates *see* Chromium Hexavalent Compounds

Appendix G: List of Substances by CAS Number

- 50-00-0 see Formaldehyde
50-18-0 see Cyclophosphamide
50-29-3 see Dichlorodiphenyltrichloroethane
50-32-8 (benzo[*a*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
50-55-5 see Reserpine
51-52-5 see Propylthiouracil
51-79-6 see Urethane
52-24-4 see Thiotepa
53-70-3 (dibenz[*a,h*]anthracene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
53-96-3 see 2-Acetylaminofluorene
55-18-5 (*N*-Nitrosodiethylamine) see *N*-Nitrosamine Compounds: 15 Listings
55-86-7 see Nitrogen Mustard Hydrochloride
55-98-1 see 1,4-Butanediol Dimethanesulfonate
56-23-5 see Carbon Tetrachloride
56-53-1 see Diethylstilbestrol
56-55-3 (benz[*a*]anthracene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
56-75-7 see Chloramphenicol
57-14-7 see 1,1-Dimethylhydrazine
57-41-0 see Phenytoin and Phenytoin Sodium
57-57-8 see β -Propiolactone
57-83-0 see Progesterone
58-89-9 (lindane) see Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
59-89-2 (*N*-Nitrosomorpholine) see *N*-Nitrosamine Compounds: 15 Listings
60-11-7 see 4-Dimethylaminoazobenzene
61-82-5 see Amitrole
62-44-2 (phenacetin) see Phenacetin and Analgesic Mixtures Containing Phenacetin
62-50-0 see Ethylmethanesulfonate
62-55-5 see Thioacetamide
62-56-6 see Thiourea
62-75-9 (*N*-Nitrosodimethylamine) see *N*-Nitrosamine Compounds: 15 Listings
63-92-3 see Phenoxybenzamine Hydrochloride
64-67-5 see Diethyl Sulfate
66-27-3 see Methyl Methanesulfonate
67-66-3 see Chloroform
67-72-1 see Hexachloroethane
68-22-4 see Norethisterone
70-25-7 (*N*-Methyl-*N'*-Nitro-*N*-Nitrosoguanidine) see *N*-Nitrosamine Compounds: 15 Listings
71-43-2 see Benzene
75-01-4 (vinyl chloride) see Vinyl Halides (Selected)
75-02-5 (vinyl fluoride) see Vinyl Halides (Selected)
75-07-0 see Acetaldehyde
75-09-2 see Dichloromethane
75-21-8 see Ethylene Oxide
75-27-4 see Bromodichloromethane
75-52-5 see Nitromethane
75-55-8 see 2-Methylaziridine
75-56-9 see Propylene Oxide
77-09-8 see Phenolphthalein
77-78-1 see Dimethyl Sulfate
78-79-5 see Isoprene
79-01-6 see Trichloroethylene
79-06-1 see Acrylamide
79-44-7 see Dimethylcarbamoyl Chloride
79-46-9 see 2-Nitropropane
81-49-2 see 1-Amino-2,4-Dibromoanthraquinone
82-28-0 see 1-Amino-2-Methylantraquinone
88-06-2 see 2,4,6-Trichlorophenol
88-72-2 see *o*-Nitrotoluene
90-04-0 (*o*-anisidine) see *o*-Anisidine and Its Hydrochloride
90-94-8 see Michler's Ketone
91-20-3 see Naphthalene
91-23-6 see *o*-Nitroanisole
91-59-8 see 2-Naphthylamine
91-94-1 (3,3'-dichlorobenzidine) see 3,3'-Dichlorobenzidine and Its Dihydrochloride
92-67-1 see 4-Aminobiphenyl
92-87-5 (benzidine) see Benzidine and Dyes Metabolized to Benzidine
93-15-2 see Methyleugenol
94-59-7 see Safrole
95-06-7 see Sulfallate
95-53-4 (*o*-toluidine) see *o*-Toluidine and Its Hydrochloride
95-69-2 (*p*-chloro-*o*-toluidine) see *p*-Chloro-*o*-toluidine and Its Hydrochloride
95-80-7 see 2,4-Diaminotoluene
95-83-0 see 4-Chloro-*o*-phenylenediamine
96-09-3 see Styrene-7,8-oxide
96-12-8 see 1,2-Dibromo-3-Chloropropane
96-13-9 see 2,3-Dibromo-1-propanol
96-18-4 see 1,2,3-Trichloropropane
96-45-7 see Ethylene Thiourea
97-56-3 see *o*-Aminoazotoluene
98-07-7 see Benzotrithloride
98-95-3 see Nitrobenzene
100-42-5 see Styrene
100-75-4 (*N*-Nitrosopiperidine) see *N*-Nitrosamine Compounds: 15 Listings
101-14-4 see 4,4'-Methylenebis(2-chloroaniline)
101-61-1 see 4,4'-Methylenebis(*N,N*-dimethyl)benzylamine
101-77-9 (4,4'-methyleneedianiline) see 4,4'-Methyleneedianiline and its Dihydrochloride
101-80-4 see 4,4'-Oxydianiline
101-90-6 see Diglycidyl Resorcinol Ether
106-46-7 see 1,4-Dichlorobenzene
106-87-6 see 4-Vinyl-1-cyclohexene Diepoxide
106-89-8 see Epichlorohydrin
106-93-4 see 1,2-Dibromoethane
106-99-0 see 1,3-Butadiene
107-06-2 see 1,2-Dichloroethane
107-13-1 see Acrylonitrile
107-30-2 (chloromethyl methyl ether) see Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
110-00-9 see Furan
115-28-6 see Chlorendic Acid
116-14-3 see Tetrafluoroethylene
117-10-2 see Danthron
117-79-3 see 2-Aminoanthraquinone
117-81-7 see Di(2-ethylhexyl) Phthalate
118-74-1 see Hexachlorobenzene
119-90-4 (3,3'-dimethoxybenzidine) see 3,3'-Dimethoxybenzidine and Dyes Metabolized to 3,3'-Dimethoxybenzidine
119-93-7 (3,3'-dimethylbenzidine) see 3,3'-Dimethylbenzidine and Dyes Metabolized to 3,3'-Dimethylbenzidine
120-71-8 see *p*-Cresidine
122-66-7 see Hydrazobenzene
123-91-1 see 1,4-Dioxane
126-72-7 see Tris(2,3-dibromopropyl) Phosphate
126-99-8 see Chloroprene
127-18-4 see Tetrachloroethylene
134-29-2 (*o*-anisidine hydrochloride) see *o*-Anisidine and Its Hydrochloride
135-20-6 see Cupferron
136-35-6 see Diazoaminobenzene
136-40-3 see Phenazopyridine Hydrochloride
139-13-9 see Nitrotriacetic Acid
139-65-1 see 4,4'-Thiodianiline
143-50-0 see Kepone
148-82-3 see Melphalan
154-93-8 bis(chloroethyl) nitrosourea see Nitrosourea Chemotherapeutic Agents
189-55-9 (dibenzo[*a,h*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
189-64-0 (dibenzo[*a,h*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
191-30-0 (dibenzo[*a,h*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
192-65-4 (dibenzo[*a,e*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
193-39-5 (indeno[1,2,3-*cd*]pyrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
194-59-2 (7H-dibenzo[*c,g*]carbazole) see Polycyclic Aromatic Hydrocarbons: 15 Listings
205-82-3 (benzo[*j*]fluoranthrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
205-99-2 (benzo[*b*]fluoranthrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings
207-08-9 (benzo[*k*]fluoranthrene) see Polycyclic Aromatic Hydrocarbons: 15 Listings

- 224-42-0 (dibenz[*a,j*]acridine) *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
 226-36-8 (dibenz[*a,h*]acridine) *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
 298-81-7 (methoxsalen) *see* Methoxsalen with Ultraviolet A Therapy
 302-01-2 (hydrazine) *see* Hydrazine and Hydrazine Sulfate
 303-47-9 *see* Ochratoxin A
 305-03-3 *see* Chlorambucil
 313-67-7 (aristolochic acid I) *see* Aristolochic Acids
 320-67-2 *see* Azacitidine
 366-70-1 *see* Procarbazine and Its Hydrochloride
 434-07-1 *see* Oxymetholone
 443-48-1 *see* Metronidazole
 446-86-6 *see* Azathioprine
 475-80-9 (aristolochic acid II) *see* Aristolochic Acids
 505-60-2 *see* Mustard Gas
 509-14-8 *see* Tetranitromethane
 513-37-1 *see* Dimethylvinyl Chloride
 542-75-6 *see* 1,3-Dichloropropene (Technical Grade)
 542-88-1 (bis(chloromethyl) ether) *see* Bis(chloromethyl) Ether and Technical-Grade Chloromethyl Methyl Ether
 556-52-5 *see* Glycidol
 563-47-3 *see* 3-Chloro-2-methylpropene
 569-61-9 *see* Basic Red 9 Monohydrate
 593-60-2 (vinyl bromide) *see* Vinyl Halides (Selected)
 608-73-1 (hexachlorocyclohexanes) *see* Lindane, Hexachlorocyclohexane (Technical Grade), and Other Hexachlorocyclohexane Isomers
 612-83-9 (3,3'-dichlorobenzidine dihydrochloride) *see* 3,3'-Dichlorobenzidine and Its Dihydrochloride
 621-64-7 (*N*-Nitrosodi-*n*-Propylamine) *see* *N*-Nitrosamine Compounds: 15 Listings
 636-21-5 (*o*-toluidine hydrochloride) *see* *o*-Toluidine and Its Hydrochloride
 680-31-9 *see* Hexamethylphosphoramide
 684-93-5 (*N*-Nitroso-*N*-Methylurea) *see* *N*-Nitrosamine Compounds: 15 Listings
 759-73-9 (*N*-Nitroso-*N*-Ethylurea) *see* *N*-Nitrosamine Compounds: 15 Listings
 924-16-3 (*N*-Nitrosodi-*n*-Butylamine) *see* *N*-Nitrosamine Compounds: 15 Listings
 930-55-2 (*N*-Nitrosopyrrolidine) *see* *N*-Nitrosamine Compounds: 15 Listings
 1116-54-7 (*N*-Nitrosodiethanolamine) *see* *N*-Nitrosamine Compounds: 15 Listings
 1120-71-4 *see* 1,3-Propane Sultone
 1314-20-1 (thorium dioxide) *see* Ionizing Radiation
 1317-95-9 (tripoli) *see* Silica, Crystalline (Respirable Size)
 1332-21-4 *see* Asbestos
 1336-36-3 *see* Polychlorinated Biphenyls
 1402-68-2 *see* Aflatoxins
 1464-53-5 *see* Diepoxybutane
 1746-01-6 *see* 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
 1836-75-5 *see* Nitrofen
 2385-85-5 *see* Mirex
 2425-06-1 *see* Captafol
 2475-45-8 *see* Disperse Blue 1
 3165-93-3 (*p*-chloro-*o*-toluidine hydrochloride) *see* *p*-Chloro-*o*-toluidine and Its Hydrochloride
 3296-90-0 *see* 2,2-Bis(bromomethyl)-1,3-propanediol (Technical Grade)
 3697-24-3 (5-methylchrysene) *see* Polycyclic Aromatic Hydrocarbons: 15 Listings
 4342-03-4 *see* Dacarbazine
 4549-40-0 (*N*-Nitrosomethylvinylamine) *see* *N*-Nitrosamine Compounds: 15 Listings
 5522-43-0 (1-nitropyrene) *see* Nitroarenes (Selected)
 7439-92-1 (lead) *see* Lead and Lead Compounds
 7440-02-0 (nickel) *see* Nickel Compounds and Metallic Nickel
 7440-38-2 (arsenic) *see* Arsenic and Inorganic Arsenic Compounds
 7440-41-7 (beryllium) *see* Beryllium and Beryllium Compounds
 7440-43-9 (cadmium) *see* Cadmium and Cadmium Compounds
 7446-34-6 *see* Selenium Sulfide
 7496-02-8 (6-nitrochrysene) *see* Nitroarenes (Selected)
 7664-93-9 (sulfuric acid) *see* Strong Inorganic Acid Mists Containing Sulfuric Acid
 8001-35-2 *see* Toxaphene
 8007-45-2 (coal tar) *see* Coal Tars and Coal-Tar Pitches
 9004-66-4 *see* Iron Dextran Complex
 10034-93-2 (hydrazine sulfate) *see* Hydrazine and Hydrazine Sulfate
 10043-92-2 (radon) *see* Ionizing Radiation
 10124-43-3 *see* Cobalt Sulfate
 10540-29-1 *see* Tamoxifen
 12001-28-4 (crocidolite) *see* Asbestos
 12001-29-5 (chrysotile) *see* Asbestos
 12172-73-5 (amosite) *see* Asbestos
 13010-47-4 (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea) *see* Nitrosourea Chemotherapeutic Agents
 13256-22-9 (*N*-Nitrososarcosine) *see* *N*-Nitrosamine Compounds: 15 Listings
 13552-44-8 (4,4'-methylenedianiline dihydrochloride) *see* 4,4'-Methylenedianiline and its Dihydrochloride
 13654-09-6 (decabromobiphenyl) *see* Polybrominated Biphenyls
 13768-00-8 (actinolite) *see* Asbestos
 13909-09-6 (1-(2-chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea) *see* Nitrosourea Chemotherapeutic Agents
 14464-46-1 (cristobalite) *see* Silica, Crystalline (Respirable Size)
 14567-73-8 (tremolite) *see* Asbestos
 14808-60-7 (quartz) *see* Silica, Crystalline (Respirable Size)
 15468-32-3 (tridymite) *see* Silica, Crystalline (Respirable Size)
 15663-27-1 *see* Cisplatin
 16543-55-8 (*N*-Nitrosomonocotine) *see* *N*-Nitrosamine Compounds: 15 Listings
 17068-78-9 (anthophyllite) *see* Asbestos
 18540-29-9 (chromium VI) *see* Chromium Hexavalent Compounds
 18883-66-4 (streptozotocin) *see* Nitrosourea Chemotherapeutic Agents
 23214-92-8 *see* Adriamycin
 23246-96-0 *see* Riddelliine
 25013-16-5 *see* Butylated Hydroxyanisole
 26471-62-5 *see* Toluene Diisocyanates
 36355-01-8 (hexabromobiphenyl) *see* Polybrominated Biphenyls
 39156-41-7 *see* 2,4-Diaminoanisole Sulfate
 42397-64-8 (1,6-dinitropyrene) *see* Nitroarenes (Selected)
 42397-65-9 (1,8-dinitropyrene) *see* Nitroarenes (Selected)
 54749-90-5 (chlorozotocin) *see* Nitrosourea Chemotherapeutic Agents
 57835-92-4 (4-nitropyrene) *see* Nitroarenes (Selected)
 61288-13-9 (octabromobiphenyl) *see* Polybrominated Biphenyls
 64091-91-4 (4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone) *see* *N*-Nitrosamine Compounds: 15 Listings
 65996-93-2 (coal-tar pitch) *see* Coal Tars and Coal-Tar Pitches
 66733-21-9 *see* Erionite
 67774-32-7 (FireMaster FF-1) *see* Polybrominated Biphenyls
 67774-32-7 *see* Polybrominated Biphenyls
 76180-96-6 (2-amino-3-methylimidazo-[4,5-*f*]quinoline [IQ]) *see* Heterocyclic Amines (Selected)
 77094-11-2 (2-amino-3,4-dimethylimidazo[4,5-*f*]quinoline [MeIQ]) *see* Heterocyclic Amines (Selected)
 77500-04-0 (2-amino-3,8-dimethylimidazo[4,5-*f*]quinoxaline [MeIQx]) *see* Heterocyclic Amines (Selected)
 105650-23-5 (2-amino-1-methyl-6-phenylimidazo[4,5-*b*]pyridine [PhIP]) *see* Heterocyclic Amines (Selected)
 108171-26-2 *see* Chlorinated Paraffins